



August 24, 2016

Wendy Cleland-Hamnett
Director, Office of Pollution Prevention and Toxics
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460-0001
Sent electronically to www.regulations.gov docket # EPA-HQ-OPPT-2016-0400

Re: ACC Comments to Inform EPA's Rulemaking on the Conduct of Risk Evaluations under the Lautenberg Chemical Safety Act

Dear Ms. Cleland-Hamnett:

The American Chemistry Council (ACC)¹ appreciates the opportunity to provide input to the Office of Pollution Prevention and Toxics to inform the Agency's development of a risk evaluation rulemaking under the Frank R. Lautenberg Chemical Safety for the 21st Century Act (LCSA). ACC has a long-standing commitment to a robust, science-based approach to evaluation of human and environmental risk. ACC is committed to the effective implementation of the LCSA and supports a workable, rigorous process that allows for timely, high quality reviews. Given the strong emphasis on a risk-based approach in the LCSA, the Section 6(b)(4) rulemaking is particularly important because it will guide the conduct of future risk evaluations that will then inform risk management activities.

ACC is committed to being a constructive stakeholder throughout the implementation of LCSA. We will continue to draw from the breadth and depth of our member companies' expertise to ensure that our recommendations are not only science-based, but also allow for the efficient and effective implementation of the LCSA. In doing so, ACC will continue to consider the high quality science standards in the LCSA as well as the timeframes and deadlines imposed therein. The enclosed recommendations were developed with these important considerations in mind.

If EPA has any questions, please contact me at nancy_beck@americanchemistry.com or 202-249-6417.

Sincerely,

A handwritten signature in dark ink, appearing to read "Nancy Beck".

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Senior Director, Regulatory and Technical Affairs

Cc: Jim Jones, OCSPP Assistant Administrator
Louise Wise, Deputy Assistant Administrator
Jeffery Morris, Deputy Director for Programs, OPPT
Tala Henry, Director, Risk Assessment Division, OPPT

¹ The American Chemistry Council (ACC) represents the leading companies engaged in the business of chemistry. More information about ACC is presented in the body of our comments.

American Chemistry Council
Initial Input to U.S. Environmental Protection Agency
In Regard to the Risk Evaluation Rule under the Lautenberg Chemical Safety Act

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I. Introduction and Executive Summary

The American Chemistry Council (ACC)² is pleased to provide the U.S. Environmental Protection Agency solicitation of written comments to be entered into the docket, well in advance of publication of the proposed rule. Our comments both clarify, as well as supplement and expand upon, the oral comments we presented at the August 9 meeting.

Under the HHS Substances Criteria (TSCA). We believe that high quality risk evaluation, using best available science and weight of the evidence (WoE), is at the very heart of the LCSA. Effective and efficient risk evaluations will help deliver the results intended by Congress.

6HFWLRQ^L 1 ♂ E□♂ 1 □♂ %□^L RI^L WKH^L VWDWXWH^L UHTXLUHV^L (3\$^L WR^L HVWDEOLV^L This certainly should include a description of the sequence of events, timelines, opportunities for public comments and peer review. Both Sections 6 and 26 of the LCSA outline various substantive elements that apply to and inform risk evaluation. A risk evaluation must:

- ☐ Be conducted in a manner designed to determine whether the chemical or substance is reasonably expected to cause or contribute to the development of cancer in humans; and
- ☐ Identify whether there exists a reasonable concern that the chemical or substance may be carcinogenic to humans, based on the results of the risk evaluation under conditions of use;
- ☐ Address the specific elements set out in Section 6(b)(4)(F); and
- ☐ Comply with the specific requirements of Section 26, including the best available science, weight of the evidence, and transparency requirements.

Because these elements are at the core of the risk evaluation process, and affect risk management measures, they are substantive and should be described in adequate detail in the regulation. In general, where risk evaluation elements are now required by statute, EPA should apply them uniformly and universally reflecting them in the body of the regulation.

The recommendations provided by ACC in these comments address screening and refined risk evaluations and are meant to apply to both human health and environmental risks. Specific tools, testing methods, databases, and the like may develop over time, or course, and can be updated as necessary in policies,

² The American Chemistry Council (ACC) represents the leading companies engaged in the business of chemistry. ACC members apply the science of chemistry to make innovative products and services that make people's lives better, healthier and safer. ACC is committed to improved environmental, health and safety performance through Responsible Care[®], common sense advocacy designed to address major public policy issues, and health and environmental research and product testing. The business of chemistry accounts for fourteen percent of all U.S. exports. Chemistry companies are among the largest investors in research and development. Safety and security have always been primary concerns of ACC members, and they have intensified their efforts, investing more than \$1 billion annually in safety and security infrastructure.

procedures and guidance. Our comments strive to make these differentiations and explain where particular elements of risk evaluation should be included in the rule proper.

Specifically, our recommendations suggest definitions, and procedural steps and elements that will allow EPA to ensure that risk evaluations are consistent with the statutory requirements for EPA to use the best available science and WoE approaches. The recommendations also include definitions and procedural steps are not expected to change over time. ACC has referenced each of our suggestions to an existing EPA guidance, a National Academies (NAS) report, or another authoritative body or peer reviewed report.)RU^L LQVWDQFH^Q ^L WKH^L UHFRPPHQGDWLRQV^L LQ^L (3\$¶V^L ± !! !! ^L 5LVN^L & KDUD practices today. Adding adequate definitions and explanation to the rule is particularly important to achieving incorporation of statutory requirements.

We also note that in addition to Section 6, Sections 26(h), 26(i), 26(j), and 26(k) of the LCSA each present legal requirements that are applicable to the risk evaluation. EPA will now need to provide a level of transparency regarding not only the inputs, but also the methods of the analysis, including clear descriptions of uncertainties and variability. EPA should leverage information from other jurisdictions where data and information is applicable and of sufficient quality to meet the science standards in the LCSA.

Incorporating these elements into the rulemaking creates a better platform for clear and consistent articulation of the Agency’s understanding of statutory requirements, and will better support consistent and uniform application of the elements of risk evaluation.

It is critically important that EPA engage the public as EPA plans, scopes, and conducts risk evaluations. Industry scientists often have unique insight and experience with their companies' chemistries and collectively have a large body of knowledge of risk assessment processes globally, including an understanding of potential human health and environmental impacts. ACC encourages EPA to leverage this knowledge and engage early (well before draft risk evaluations are released) and frequently with industry throughout the risk evaluation process.

II. The Risk Evaluation Rulemaking Must Include both Procedural and Substantive Elements to Effect the Purposes of the Statute

Congress included a specific mandate to EPA to establish a risk evaluation rulemaking. There is little question that the rule must describe the process by which risk evaluations will be conducted.³ However, to effect the purposes of the statute, the process described in the rule cannot merely set out timelines or the sequence of the risk evaluation. It must include a clear articulation of the substantive elements of risk evaluation, and more particularly, it must explain how it will apply the principles set out in Section 6(b)(4)(F), Section 26, and other parts of the statute. If Congress had intended the scientific standard of

³ EHVW^L DYDLODEOH^L VFLHQFH^L RU^L ³ ZHLJKW^L RI^L WKH^L VEHUQWH^L HYLGH^L
ZRXOG^L KDYH^L LOFOXGHG^L WKHP^L ROO^L \ LO^L 6HFWLRO^L \ O^L RO^L ³ SROLFL

3 > 77 KSGPLQLVWUDWRU^L VKDOO^L HWVDEOLVK^Q ^L E \ ^L UXOH^Q ^L D^L SURFHVV^L WR^L FRQGXF^L ULVN^L
Section 6(b)(4)(A).

The very purpose of the risk evaluation is to develop the evidentiary and scientific basis to enable EPA to complete the risk determination required by statute. That risk determination has substantive impact if it significantly affects conduct, activity or a substantive interest that is the subject of agency regulation. The determination following risk evaluation is a necessary prerequisite for a chemical to proceed to risk management, if warranted. The rule should thus include a clear description of how EPA will undertake risk evaluations in order to meet the new statutory requirements of the LCSA. This includes a description of the scoping process and requirements for a published scope as well as the elements of the risk evaluation itself and the mechanism for gauging adequacy as measured against statutory criteria.

III. The Proposed Rule Should Include a Tiered Approach to Risk Evaluation

We believe the statute contemplates a tiered approach to risk evaluation and recommend that EPA include a tiered approach in the rule. Under the LCSA, (3)§ 1052(a)(1) a chemical is a high-priority substance if it is a carcinogen, a chemical that causes or may cause serious or irreversible effects, or a chemical that presents a significant risk of injury to health or the environment. The scope, however, LV 1052(a)(2) QRW 1052(a)(3) UHTXLUHG 1052(a)(4) WR 1052(a)(5) EH 1052(a)(6) SXEOLV K 1052(a)(7) L QLWLDWLRQ has up to six months following the initiation of the risk evaluation to prepare and publish the scope. Congress intended this six month period to be used for a scoping exercise, where EPA identifies 3 What hazards, exposures, conditions of use, and the potentially exposed or susceptible subpopulations the Administrator expects to consider in the risk evaluation 4 7 KLV 1052(a)(8) VL 1052(a)(9) PRQWK 1052(a)(10) SH 1052(a)(11) VWHS 1052(a)(12) EHWZHHQ 1052(a)(13) WKH 1052(a)(14) KL J K 1052(a)(15) SULRULW of the scope. J QDWLRQ 1052(a)(16) DQG 1052(a)(17) WKH 1052(a)(18) SXE

In order for EPA to conduct risk evaluations consistent with the quality required by the LCSA and within the timeframes required, EPA should conduct a screening level evaluation during the scoping phase. During the scoping phase of risk evaluations, tools exist to allow EPA to conduct quantitative screening level analyses of multiple exposure scenarios, as appropriate for consumers, sensitive subpopulations, and the environment. This will allow EPA to have a more tailored focus on those populations and exposures of greatest concern during a refined risk evaluation process. Figure 1 below depicts ACC ¶ 1052(a)(19) recommended approach.

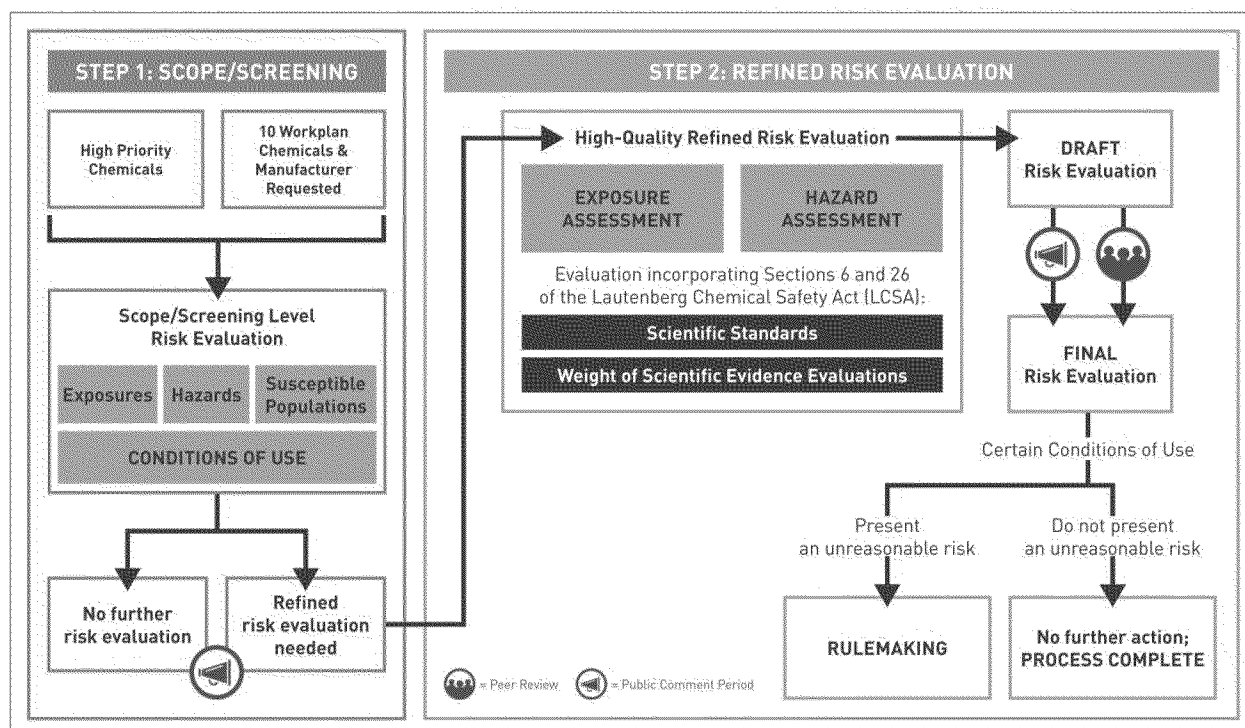


Figure 1. A Two-Step Process for Conducting Risk Evaluations

Note: This is a simplified version of the process.

A tiered approach, where EPA uses the scoping step (step 1) to conduct a quantitative screening level analysis, will allow EPA to focus its limited resources on more robust refined risk evaluations for only those conditions of use where unreasonable risks cannot be ruled out. Screening-level assessments require less data and information, and are typically deterministic and based on conservative, health protective assumptions and methods. When a screening assessment indicates low risk for a particular condition of use, the Agency should have a high degree of confidence that the potential risks are much lower than the calculation and, therefore, the actual risks are lower and/or perhaps non-existent. However, when a screening-level risk assessment indicates a potential concern for an adverse effect, this does not mean that the actual risks are significant and warrant action. Rather, it indicates the Agency should take a second step in the risk evaluation process to refine the evaluation to more accurately quantify potential risks.

The refined risk evaluation (step 2) will require realistic and representative data, higher tier modeling approaches, including probabilistic exposure modeling, and a more comprehensive consideration of human relevance and dose-response relationships. In a refined evaluation, EPA should also consider targeted exposure studies, as well as biomonitoring and environmental monitoring data, to the extent that this information is available and relevant. This approach is consistent with (3§ ¶ V^L ± !! ¶ |^L) UDPH Z RUN^L IRU Health Risk Assessment to Inform Decision Making (HHRA Framework)⁴, which also emphasizes the importance of a fit-for-purpose approach to risk evaluation. This approach is also consistent with (3§ ¶ V^L exposure assessment guidelines and practices.⁵ The concept of a tiered approach and a fit-for-purpose evaluation are woven throughout ACC ¶ Recommendations.

⁴ See <https://www.epa.gov/sites/production/files/2014-12/documents/hhra-framework-final-2014.pdf>.

⁵ See: <https://www.epa.gov/expobox/exposure-assessment-tools-tiers-and-types-screening-level-and-refined>.

The tiered approach ACC recommends is consistent with the approach EPA took in the problem formulation and initial assessment document for tetrabromobisphenol A (TBBPA).⁶ In that document, EPA conducted an initial screening level evaluation to support its conceptual model and analysis plan. EPA appropriately used high-end exposure values coupled with the lowest toxicity values to evaluate uses and exposure pathways of potential concern. While EPA did not share the relevant risk evaluation calculations in its public document, the general approach is consistent with that of a screening level risk evaluation. ACC encourages EPA to continue with this approach and to transparently and clearly present quantitative screening level analyses for the conditions of use and exposure scenarios that are part of the conceptual model EPA develops as part of the scoping phase.

IV. The Rule Should Clarify the Process for Preparation and Contents of the Scope

As noted above, Congress allowed a six month period for preparation of the scope of the risk evaluation, contemplating that time and effort would be needed to move from prioritization to a published scope. The six month period is to enable EPA to identify potentially exposed or susceptible subpopulations the Administrator expects to consider in the risk evaluation. The language in the bill from which this provision is derived: 1) EPA should use this period to evaluate and decide which, if any, potentially exposed or susceptible subpopulations should be included in the risk evaluation (in other words, it need not include all such subpopulations, regardless of size, impact, or relevance); and 2) EPA has flexibility to actually conduct a full risk evaluation of some or all the potential scenarios set out in the scope.

In short, EPA need not include every conceivable condition of use in a risk evaluation. This view is consistent with the need for EPA to determine the relevant conditions of use: Section 6 of the LCRA, which provides that the Administrator, under which a chemical substance is intended, known, or reasonably foreseen to be represented by the

V. The Proposed Rule Should Include a Detailed Description of Substantive Elements of Risk Evaluation

Section 6 of the LCRA, which provides that the Administrator, under which a chemical substance is intended, known, or reasonably foreseen to be represented by the term "integrated hazard" (integrating hazard with exposure) in the LCRA, EPA is encouraged to explicitly define and operationalize this term as part of its rulemaking. The term will not have clear meaning until an interpretation is assigned by EPA. We believe the essential elements of a Section 6 and 26 risk evaluation must be articulated in a clear regulatory definition as we discuss below.

⁶ EPA, Problem Formulation and Initial Assessment Tetrabromobisphenol A and Related Chemicals Cluster Flame Retardants, 2015, available at: <https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/tsca-work-plan-chemical-problem-formulation-and-2>.

6HFWLRQ^L 1 8 E 8 1 8 % 1 RI^L WKH^L VWDWXWH^L UHTXLUHV^L (3\$^L WR^L HVWDEOLV^L. This process is itself required to meet a number of substantive elements described in the LCSA; a risk evaluation must:

%H^L FRQGXFWHG^L LQ^L D^L PDQQHU^L GHVLJQH^L WR^L KHOS^L WKH^L DJHQF^L VXEWDQFH^L SUHVHQW^L DQ^L XQUHDVRQDEOH^L ULVN^L RIs to QM\ \^L WR^L Section 6(b)(4)(A).
,QFOXGH^L FRQVLGHUDWLRQ^L RIs to DQ^L XQUHDVRQDEOH^L or susceptible
VXESRSXODWLRQ^L 1^L (3\$^L PXVW^L LGHQWLI^L \^L UHOHYDQW^L SRWHQWLDOO^L relevant to the risk evaluation under conditions of use;
Address the specific elements set out in Section 6(b)(4)(F); and
Comply with the specific requirements of Section 26, including the best available science, weight of the evidence, and transparency requirements.

The very purpose of the risk evaluation is to develop the evidentiary and scientific basis to enable EPA to complete the risk determination required by statute. That risk determination has substantive impact ±it significantly affects conduct, activity or a substantive interest that is the subject of agency regulation. The basis for the risk determination thus should be adequately described in the rule itself to offer sufficient notice to the regulated community. This is particularly important for decisions that inform safety and safety determinations.⁷ Likewise, decisions that have broad reaching impact should be supported in regulations, not merely through guidance or agency policy.⁸ While EPA cannot substitute policy or guidance for a regulatory description of what will constitute a complete and robust risk evaluation, we believe the necessary elements can be developed in this rulemaking in a timely manner.

VI. The Proposed Rule Should Ensure Consistency with Section 6(b)(4)(F)

As discussed below, Section 6(b)(4)(F) of the LCSA describes five requirements for risk evaluations that shall be considered by the Administrator and must be incorporated into the risk evaluation rulemaking.

⁷ See, e.g., *MST Express v. U.S. Department of Transportation*, 108 F.3d 401 (D.C. Cir. 1997). DOT was directed under the ORWRU^L & DUULHU^L 6DIHW^L \^L \$FW^L 0 & 6\$^L WR^L 3 SUHVWDQFH^L to UHTXLUHV^L RIs to QM\ \^L WR^L DQG^L RSHUDWRUV^L RI^L FRPPHUFLDO^L PRWRU^L YHKLFOHV^L 1^L that (RIs to QM\ \^L WR^L 7KH^L 0 & 6\$^L LQFOXGH^L 3 D^L PHDQV^L RI^L GHFLGLQJ^L J^L Z KHWKHU^L WKH^L RZQHUV^L RSHUDWRUV^L DQG^L SHUVRQ^L promulgated regulations that set out a process for decision making but used guidance to articulate the tests by which the agency ZRXOG^L GHWHUPLQH^L Z KHWKHU^L YHKLFOHV^L PHW^L WKH^L VDIHW^L \^L ILWQHVV^L UHTXLUHPHQWV^L 1^L LW^L 3 IDLOHG^L WR^L FDUU^L \^L RXW^L LWV^L VWDWXWRU^L \^L REOLJDWLRQ^L WR^L aRWHDEOLVK^L \^L UHJX^L ZLWK^L WKH^L VDIHW^L \^L ILWQHVV^L UHTXLUHPHQWV^L 1^L .
⁸ \$V^L D^L JHQHUDO^L RIs to QM\ \^L WR^L 3 SUHVWDQFH^L to UHTXLUHV^L RIs to QM\ \^L WR^L 7KH^L 0 & 6\$^L create law, usually complementary to an existing law. *Gibson Wine Co. v. Snyder*, 194 F.2d 329, 331 (D.C. Cir. 1952), cited by *Brown Express, Inc. v. U.S.*, 607 F.2d 695, 700 (5th Cir. 1979). \$^L 3 UXOH^L \^L LV^L GHWHUPLQH^L by the Administrative Procedure Act, in relevant part, DV^L 1^L 3 WKH^L Z KROH^L RIs to QM\ \^L WR^L 7KH^L 0 & 6\$^L applicability and future effect designed to implement, interpret, or prescribe law or policy or describing the organization, procedure, or practice requirements of an agency 1^L 5 U.S.C. § 551(4).

a. Integration and Assessment of Information Relevant to Risks and Information on Potentially Exposed and Susceptible Populations

Section 6(b)(4)(F)(i) requires risk evaluations to integrate and assess available information on hazards and exposures for the conditions of use of the chemical substance. The statute does not, however, explain how information will be integrated or how it will be assessed. The process of how and when information will be integrated and assessed should be described in the proposed rule.

There are two key considerations in section 6(b)(4)(F)(i).⁹ First, EPA must integrate and assess information for conditions of use that are relevant to risks to human health and the environment, and second, EPA must provide information on potentially exposed or susceptible subpopulations identified as relevant.

i. Conditions of Use That are Relevant

As discussed above, had Congress intended EPA to necessarily address all conditions of use of a chemical, it would have required EPA to do so. EPA should not include exposure scenarios that are in clear violation of OSHA workplace limits or EPA regulatory requirements, exposures that are not consistent with labeling requirements for safe use, or exposures that are inconsistent with intended uses of consumer products. In addition, EPA should not include exposure scenarios regulated under other federal laws.

ii. Potentially Exposed or Susceptible Subpopulations

Section 6(b)(4)(F)(i) requires EPA to integrate and assess information on potentially exposed or susceptible subpopulations identified by EPA as relevant to the risk evaluation. In the proposed rule, EPA should describe the process it will use to identify subpopulations and how it will make a determination that the subpopulation is relevant to the risk evaluation. The VWDWXWH^L GRHV^L RIIHU^L D^L GHILQLWLRQ^L RI^L ³ SRWHQWLDQ Section [S₁ ♂ ¶^L □^L WKDW^L FODULILHV^L WKDW^L WKH^L VXESRSXODWLRQ^L PXVW^L H[SRVXUH^L ' ^L WR^L D^L FKHPDFDO^L VXEVWDQFH^L RU^L PL[WXUH^L DQG^L C general population.¹⁰ While this is helpful, it is not sufficient to inform the risk evaluation process.

⁹ Section 6(b)(4)(F)(i) states that EPA must “consider the conditions of use of the chemical substance, including information that is relevant to specific risks of injury to health or the environment and information on potentially exposed or susceptible subpopulations identified as relevant by the Administrator.”

general population identified by the Administrator who, due to either greater susceptibility or greater exposure, may be at greater risk than the general population of adverse health effects from exposure to a chemical substance or mixture, such as infants, children, pregnant women, workers, or the elderly.

TKH^L WHUP^L ³ SRWHQWLDOO \ ^L H[SRVHG^L (3\$^L V^L FODULILFDWLRQ^L LQ^L WK^L ,W^L PRGLILHV^L ³ VXSRSXODWLRQ^L ' ^L DQG^L ZH^L GR^L QRW^L EHOLHYH^L &RQ^L VXSRSXODWLRQ^L ' ^L WR^L PHDQ^L DQ^L \ ^L VXSRSXODWLRQ^L ' ^L ZLWKRXW^L ERX^L could be conceived. A subpopulation presumably does not mean any two people anywhere who might be exposed to as little as one molecule of a chemical substance for a millisecond pursuant to a non-authorized use; or that a predator animal will spend its entire life receiving exposures from a single soil boring. An expansive view of potential exposure would make risk evaluations difficult to scope, would defeat the purposes of disciplined and methodical risk evaluation, and would impede their timely completion. Such an approach also runs counter to Congressional intent that the Agency focus on unreasonable risk, not every conceivable risk to every conceivable population. Thus, a risk evaluation should exclude potentially exposed subpopulations where the potential exposure is such that negligible risks are implicated. It would be helpful to define the term in the in the proposed rulemaking to ensure alignment with the LCSA intent.

We also note that WKH^L WHUP^L ³ SRWHQWLDOO \ ^L H[SRVHG^L would not be in alignment with WKH^L ³ J UHLDWHU^L H[SRVHG^L SURYLVRQ^L ◀ ^L 7KH^L ILUVW^L WHUP^L FRQFHSW^L second with actual exposure (and for that matter, actual exposure that exceeds the actual exposure of the general population). The proposed rule should offer this clarification. To integrate Section 26 science requirements, an explanation can be added in the proposed rule to explain what constitutes best available exposure science for purposes of reaching an agency decision as to what 'potentially exposed' means. For example, if a statistical probability of exposure is calculated or exposure modeling used, or biomonitoring data is used in a subpopulation as a proxy for exposures, the decision to use a particular approach should be outlined in the risk assessment and accompanied with an explanation of why the approach satisfies the best available science requirement.

7KH^L WHUP^L ³ J UHLDWHU^L VXFHFWLELOLW^L \ ^L LV^L D^L GLIIHUHQW^L FRQFHSW^L WKDQ^L ³ J UHLDWHU^L H[SRVHG^L (3\$^L WR^L H[SODLQ^L WKDW^L ³ J UHLDWHU^L VXFHFWLELOLW^L \ ^L PHDQV^L JURXS^L with greater potential for adverse health effects, or due to greater sensitivity) to the same chemical exposure. It would also be helpful for EPA to explain that its determination that a JURXS^L KDV^L ³ J UHLDWHU^L VXFHFWLELOLW^L \ ^L FDQQRW^L EDVHG^L RQ^L evidence, but must be founded on high quality science consistent with the best available science, weight of the evidence, and other requirements of Section 26.

:H^L DOVR^L HQFRXUDJH^L (3\$^L WR^L FRQVLGHU^L GHILQLQJ^L J^L VahleffoWHUP^L ³ J range to group size based on accepted criteria. Micropopulations of groups as small as two or three individuals, while conceivable in the abstract, would generally not exist or be identifiable in a risk evaluation exercise. It would be helpful for EPA to clarify in the rule that the term ³ JURXS^L ' ^L VKRXOG^L EH^L UHJUH^L WRJHWKHU^L ZLWK^L ³ VXSRSXODWLRQ^L ' are statistically large enough to justify identification and support the throughput objectives of the statute for risk evaluations. Examples of subpopulations identified in epidemiological and exposure science may be particularly helpful here.

b. Aggregate and Sentinel Exposures

While the plain language of the statute makes clear that aggregate or sentinel exposures need not be considered at all in the risk evaluation, EPA has discretion to do so.¹¹ If they are considered, Section 6(b)(4)(F)(ii) requires EPA to describe the basis for that consideration. We believe EPA should include definitions of both aggregate and sentinel exposures in the proposed regulation so the regulated community will understand how EPA intends to apply the terms, and to ensure consistency and regularity in application.

i. Aggregate Exposures

&RQVLVWHQW^L ZLWK^L (3\$¹Y¹²EHFHHXUHQWROH¹ aggregate exposures as the combined exposure for one substance over multiple exposure pathways from multiple different sources. As noted above, while EPA is not required to conduct aggregate exposure assessments, aggregate exposure assessment may be appropriate when available data are of sufficient quality, reliable, and representative of intended, known or reasonably foreseen exposures.

ii. Sentinel Exposures

A sentinel exposure should be thought of as the exposure that is judged to cause the plausible upper-bound individual human exposure to a substance of interest within a broad category. For example, a broad category would be air care products, which contains subcategories of air care instant action (aerosol sprays) and air care continuous action (solids and liquids) products. If the estimated exposure for the sentinel product in a broad category results in an acceptable risk assessment outcome when compared with the appropriate hazard reference value, then there is no need to continue estimating the exposure for the different subcategories. Evaluating sentinel exposures first, during a screening level evaluation in the scoping phase, will allow EPA to focus on exposures of the greatest relevance and importance, within a particular category of exposures. This is not intended to mean, for instance, that high-end occupational exposure is sentinel for consumer exposure. Rather, it can be used in an overall Product Category context ± where a sub-category with highest exposure can represent or be the sentinel for other subcategories. If the sentinel sub-category is adequately protected, then the rest are seen as acceptable. This approach is consistent with the approaches and guidance of ECHA for REACH chemical evaluations¹³ and the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC).¹⁴

¹¹ 6HFWLRQ | ♂ E □ ♂ | □ ♂) □ ♂ LL □ | described whether aggregate of sentinel exposures to a chemical substance under the conditions of use were considered, and the basis for that consideration ◀ , L L

¹² See: <https://www.epa.gov/expobox/exposure-assessment-tools-tiers-and-types-aggregate-and-cumulative>.

¹³ See ECHA Guidance on information requirements and chemical safety assessment Chapter R.15: Consumer exposure estimation, November 2009 (version 2 Rev.:0.0), available at: https://echa.europa.eu/documents/10162/13632/r15_update_version_2_rev00_en.pdf.

¹⁴ See Addendum to ECETOC Targeted Risk Assessment Report No. 93, 2009, available at: <http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-107-Addendum-to-ECETOC-TRA-report-93.pdf>.

c. Exposure Assessment

Under the LCA, to ensure a high quality exposure assessment is made clear in Section 6(b)(4)(F)(iv) and EPA must ensure that these quality characteristics are incorporated into the rulemaking.¹⁵ Understanding duration, intensity, and frequency are key elements of ensuring that the exposure assessment is robust and goes beyond the screening level. However, as covered in multiple authoritative reports and guidance documents, when considering exposure, either to humans or the environment, there are many other aspects that EPA must consider to be consistent with the high quality requirements of both Section 6 and 26 of the LCSA.

For instance, consistent with EPA exposure guidance, exposure should also consider physicochemical properties, distribution, and fate in the environment, including products of metabolism and chemical break down products.¹⁶ Sufficient, reliable data should be used over default assumptions and if models are used to estimate exposure, their strengths and limitations must be clearly described and sufficient information must be made available to enable others to replicate and verify the modeling.¹⁷ EPA must take extra care to provide clear rationales for the use of any default assumptions.¹⁸ To ensure consistency with Section 26 requirements, and best practices, EPA must clearly define uncertainties and conduct a sensitivity analysis to evaluate the impacts of individual parameters on the exposure conclusions.¹⁹

In addition, to be consistent with a WoE approach, all sources of exposure information must be described and evaluated for quality and reliability, to ensure reliance on the highest quality information. As mentioned previously, for refined risk evaluations, consistency with the best available science means that EPA should strive to use probabilistic approaches and the presentation of results should ensure that distributions of exposure, including central estimate and reasonable maximum exposure (RME) estimates are clear.²⁰ Pharmacokinetic information, biomonitoring information, and environmental monitoring information should be integrated into the assessment when it is of sufficient quality and available.²¹ Finally, if only minimal information is available to assess exposure, EPA should identify any additional information needs.²²

Consistent with the Section 26 requirement to use the best available information, we encourage EPA to use probabilistic approaches that rely on high quality data. A probabilistic approach will prevent over-reliance on data points that represent the tails of distributions and may not be stable or reproducible. In the presentation on August 9, 2016, EPA noted that for occupational exposures, high-end estimates of exposure would include the 95th or

¹⁵ 6HFWLRQ L 1 8 E 8 1 8 8) 8 8 LY 8 L VWDWHV L WKDW L WKH L \$GPLQLVWUDWRU L VKDOO L 3 WDNH L L frequency, and number of exposures under the conditions of use of the chemical substance. 8 L L

¹⁶ EPA Guidelines for Exposure Assessment, 1992 8 3 (3\$ L ([SRVXUH L * XLNOLQHV 8 8 8 https://www.epa.gov/sites/production/files/2014-11/documents/guidelines_exp_assessment.pdf.

¹⁷ Ibid.; Fenner-Crisp PA, Dellarco VL., Key Elements for Judging the Quality of a Risk Assessment, Environ Health Perspect. 2016 Feb 5, available at: <http://ehp.niehs.nih.gov/wp-content/uploads/124/8/ehp.1510483.alt.pdf>.

¹⁸ Ibid.

¹⁹ Ibid.

²⁰ National Research Council, National Academy of Sciences, Models in Environmental Regulatory Decision Making, 2007, available at <http://www.nap.edu/catalog/11972/models-in-environmental-regulatory-decision-making>; Fenner-Crisp and Dellarco, 2016.

²¹ EPA Exposure Guidelines.

²² Ibid.; Fenner-Crisp and Dellarco, 2016.

99th percentiles.²³ We note that, for occupational exposures under REACH, ECHA finds the 75th or 90th percentiles to be appropriate, particularly focusing on the 75th percentile for two situations: when measured data may represent worst case exposure activities rather than typical (air monitoring is usually performed on the tasks with highest potential for exposure) or when measured data may be high quality and represent narrow exposure conditions with consistent operational conditions and risk management measures.²⁴ When conducting refined risk evaluations, ACC encourages EPA to make these determinations using situation specific information to produce estimates that are realistic and reliable. We also encourage EPA to continue to improve the transparency and clarity of exposure assessments, ensuring that all default assumptions and uncertainties are clearly articulated.

d. Weight of the Evidence

Section 6(b)(4)(F)(v) requires a description of the WoE evaluation for both hazard and exposure and Section 26(i) requires that EPA make decisions under sections 4, 5, and 6 based on the weight of the scientific evidence.²⁵ Section VIII below will discuss this requirement in further detail.

VII. The Proposed Rule Should Incorporate Section 26(h) Scientific Standards

Risk evaluations and the risk evaluation process - must satisfy the specific requirements of Section 6, but also must satisfy the requirements of Section 26. Section 26 must be read in tandem with Section 6 requirements to effect the purpose and intent of the LCSA and must be incorporated into the rulemaking.

Risk evaluations and the risk evaluation process must comply with the best available science provision in Section 26(h) of the LCSA, as well as the WoE provision at 26(i) and the transparency provision at 26(j). Sections 26(h), 26(i), and 26(j) of the LCSA are fully consistent with the descriptions provided in the Senate Report.²⁶

²³ See slide 36 available at: https://www.epa.gov/sites/production/files/2016-08/documents/risk_evaluation_9_august_2016.pdf.

²⁴ See ECHA Guidance on Information Requirements and Chemical Safety Assessment Part R.14: Occupational exposure assessment Draft (Public) Version 3.0 November 2015, at page 23, available at: https://echa.europa.eu/documents/10162/13564/r14_draft_for_public_en.pdf. This is also consistent with the most recent final consultation update available at: https://echa.europa.eu/documents/10162/13564/r14_caracal_en.pdf/18442141-4b1a-41cb-b2eb-c619aae9fcb5.

²⁵ Section 26(h)(1) of the LCSA requires that EPA make decisions under sections 4, 5, and 6 based on the weight of the scientific evidence.

²⁶ Senate Report 114-67 states, at page 8-9, that the rulemaking should address variability, uncertainty, the degree of independent verification and peer review. The section also requires that decisions be based on the weight of the scientific evidence, by which the Committee intends that EPA consider all information in a systematic and integrative framework to consider the relevance of different information, standardized test design and methods, consistent data evaluation procedures and good laboratory practices to ensure the quality of the data. <https://www.congress.gov/114/crpt/srpt67/CRPT-114srpt67.pdf>.

Beyond including a definition of best available science in the rulemaking itself, EPA should include in its proposed rule the elements that will be considered in a best available science review. We encourage EPA to review Fenner-Crisp (2016), *Key Elements for Judging the Quality of a Risk Assessment*,²⁸ the ACC Principles for Improving Chemical Hazard and Risk Assessments (see Appendix A),²⁹ and other principles and elements described in these comments, to illustrate best available science for inclusion in the proposed rulemaking. These principles and practices are not expected to change over time. As such, EPA should have no concerns incorporating them into the risk evaluation rulemaking.

Section 26(h)(1) is intended to ensure that the information, approaches, methods and models used are appropriate for the intended use of the information.³⁰ Consistent with the two-step tiered framework ACC proposes (discussed in Section III, above) where a screening level evaluation is conducted in the scoping phase, and a more refined risk evaluation is conducted to directly inform risk management activities, when FRQVLGHUL Q J^L WKH^L EHVW^L DYDLODEOH^L - VFF SXUSRVH^L XVH^L LQWRQH^L DWK^L DFWLRQ^L HQFRUG^L EXERCISE care when including or excluding information. There may be a bias in favor of including information and data simply because it has been peer reviewed or is performed under GLP. There may also be a bias against information and data which is not. Neither bias is correct. EPA will need to consider other factors that may also be important and contribute to identifying best-available and high quality information for the specific evaluation being conducted.

A default-based, conservative model may be appropriate for a screening evaluation. However, the best available science for a refined risk evaluation requires high quality, reliable data be used over defaults, when available, and that any default assumptions that are used must be appropriate for the decision being made. 7 KLV¹ DSSURDF K¹ LV¹ Z HOO¹ HIRWOLaQhG¹ Q¹ The 3216¹ Environmental Health Perspectives (EHP) publication by Drs. Fenner-Crisp and Dellarco refers back to recommendations made as early as 1997 where the Presidential/Congressional Commission

³¹ See <https://www.epa.gov/sites/production/files/2014-12/documents/hhra-framework-final-2014.pdf>.

on Risk Assessment and Risk Management discussed the need for the complexity and depth of an assessment to be commensurate with the decision being made.³² ACC encourages EPA to follow the overarching process that is described in these documents.

b. Consideration of Relevant Information

Section 26(h)(2) stresses the importance of the consideration of relevant information.³³ That is, the scientific information must be relevant to human or environmental health. This is particularly important for the refined risk evaluations that will be used to inform risk management controls for particular uses. These controls could be as rigorous as a ban, or a costly labeling requirement, thus the highest quality data and methodologies must be used. Two areas where EPA will need to improve its consideration of relevant information, for refined risk evaluations, are hazard assessment and dose-response.

i. Improving Hazard Assessment

Sections 26(h) and 26(i) collectively require that the risk evaluation rulemaking ensure LPSURYHPHQWV¹ LQ² (3\$¶V³ FXUHQW⁴ DSSURDFK⁵ WR⁶ KDJDUG⁷ DVVHVVF assessments that will be used to inform risk management decisions in Section 6(c). EPA may be tempted to rely on data from existing databases. However, the requirements of the new statute make this very challenging. For instance, it is well known that the EPA IRIS program has been struggling for years to produce high quality assessments. The National Academies (NAS) has commented on this, criWLFDOO⁸ \⁹ QRWLQJ¹⁰ ¹¹ SHUVLVWHQW¹² SUREOHPV¹³. While the IRIS program is working to address these systemic problems, the program has, to date, not finalized a single IRIS assessment that is fully consistent with the 2011 recommendations of the NAS. As the IRIS program only releases a few final assessments a year, this means that the majority of information in the IRIS database may be outdated and not representative of the best available science, and the assessment processes used to evaluate, judge, and synthesize information may not be consistent with the best scientific evaluation practices that exist today. All of these concerns have been well articulated by the NAS.

While the risk evaluation approach currently used by OPPT does not require the direct adoption of RfDs and RfCs from IRIS, OPPT must be extremely cautious when relying on studies, points-of-departure, or endpoints simply because they were identified in an IRIS assessment. This justification will not suffice under the scientific requirements in the LCSA. Similarly, modeling approaches used by IRIS may not be fully informed by the weight of the evidence, including a review of mode of action information and mechanistic data. While relying on studies and data from IRIS may be appropriate for screening level assessments, OPPT will need to conduct new WoE evaluations for hazard identification in the refined risk evaluation process. Simply selecting the lowest value because it is health protective, regardless of quality and relevance, is not acceptable under the LCSA.

³² Fenner-Crisp and Dellarco, 2016.

33 6HFWLRQ^L ⊥ ⊥ ⊥ ⌊ ⌊ K □ ♂ ⊥ □^L VWDWHV^L WKDW theK^LEnt tSG^LPLQ theW^LUDW^LReh isV^LK^LDaD^LForReQ^LiveG^Lthe^L 3
Administrator in making a decision about a chemical substance or mixture ◀

Administrator in making a decision about a chemical substance or mixture.

34. 6H₁₀⁺ IRU⁺ H⁺DPDSOH⁺ FKDSWHU⁺ → RI⁺ WKH⁺ 1S6⁺ 5HYLHZ⁺ RI⁺ (3S⁺¶V⁺, 5,6⁺SVVHVVPHQW⁺ RI⁺)R⁺

<http://www.nap.edu/catalog/13142/review-of-the-environmental-protection-agencys-draft-iris-assessment-of-formaldehyde>

Fortunately, many authoritative bodies and government documents provide suggestions for the improvement of hazard assessment, including some EPA guidance documents. ACC encourages EPA to incorporate the five elements described in Appendix B³⁵, PSURY L Q J^L + D]DU Assessment, 'which would provide significant improvements to hazard assessment and help to HQ VXUH^L (3\$ ¶ V^L FRQVLVWHQF \^L Z LWK^L WKH^L /&6\$◀^L :H^L UHFRPPHQG^L W incorporated into the risk evaluation rulemaking. These elements have not changed over time and are not expected to change, thus EPA should not have concerns incorporating them into the risk evaluation rulemaking.

ii. Improving Dose Response Assessment

As EPA will be providing quantitative estimates of risk to inform the decision of whether risk management is necessary, a high quality dose-response assessment will be an important HOHPHQW^L RI^L (3\$ ¶ V^L UHILQHGSigificant guidance documents provide a framework to ensure that dose-response evaluations are consistent with the LCSA. ACC provides nine recommendations, including references, in Appendix C³⁶, PSURY L Q J^L 'RVH^L 5 HVSRQVH^L Assessment, 'for refined risk evaluations that should be incorporated into EPA ¶ rulemaking for risk evaluation. These elements of a high quality dose response assessment are not expected to change over time.

iii. Reliance on Guidance

While significant guidance exists on best practices regarding the process of conducting a risk evaluation, EPA must ensure that any reliance on a guidance document is consistent with the best available science. EPA guidance documents are grounded in principles of public health protection. As discussed by EPA in the 2004 Staff Paper on Principles and Practices, EPA ensures that risk is not likely to be underestimated and default assumptions are used in risk assessments to pursue this goal.³⁵ As such, when EPA refers to guidance documents, particularly older documents, EPA must ensure they are relying on science, not necessarily defaults. If EPA is relying on defaults, EPA must ensure that these default assumptions are still consistent with today ¶ best available science. For example, in the presentation on August 9, 2016, EPA pointed to the 1991 Guidelines for Developmental Toxicity Risk Assessment. (3\$ ¶ V^L FXUUHQWpolicies is based on an assumption that was articulated in 1991.³⁶ EPA must ensure that the 1991 guidance assumption is still appropriate today; it cannot simply be presumed to be accurate. EPA must now take into account all the new general and chemical-specific evidence (including pharmacokinetic data), methodological study designs for

³⁵ EPA Staff Paper on Risk Assessment Principles and Practices, 2004, available at: <https://nepis.epa.gov/Exe/ZyNET.exe/100045MJ.TXT?ZyActionD=ZyDocument&Client=EPA&Index=2000+Thru+2005&Docs=&Query=&Time=&EndTime=&SearchMethod=1&TocRestrict=n&Toc=&TocEntry=&QField=&QFieldYear=&QFieldMonth=&QFieldDay=&IntQFieldOp=0&ExtQFieldOp=0&XmlQuery=&File=D%3A%5Czyfiles%5CIndex%20Data%5C00thru05%5CTxt%5C00000007%5C100045MJ.txt&User=ANONYMOUS&Password=anonymous&SortMethod=h%7C-&MaximumDocuments=1&FuzzyDegree=0&ImageQuality=r75g8/r75g8/x150y150g16/i425&Display=hpfr&DefSeekPage=x&SearchBack=ZyActionL&Back=ZyActionS&BackDesc=Results%20page&MaximumPages=1&ZyEntry=1&SeekPage=x&ZyPURL#>.

³⁶ (3\$^L * XLGHOLQH V^L IRU^L 'HYHORSPHQWDO^L 7R[LFLW \^L 5 LVN^L \$VVHVVPHQWdevelopmental toxic DW^L SD J H effects, a primary assumption is that a single exposure at a critical time in development may produce an adverse developmental effect, i.e., repeated exposure is not a necessary prerequisite for developmental toxicity to be manifested. VWHG◀^L ' ^L \$YDLODEOH^L DW https://www.epa.gov/sites/production/files/2014-11/documents/dev_tox.pdf.

developmental assessment, and study quality criteria that may exist to inform the use of this default approach.

c. Importance of a High Quality Risk Characterization

Section 26(h)(3) speaks to the importance of clearly documenting the data and approaches used in the risk evaluation, including, but not limited to the methods, assumptions and quality assurance approaches used to generate the information.³⁷ For risk evaluation, this requirement ensures that steps are taken to provide a very clear risk characterization section in each refined risk evaluation. This step must be incorporated into the risk evaluation rule and we strongly encourage EPA to fully implement the recommendations in the 2000 EPA Risk Characterization Handbook.³⁸ ACC has identified key aspects of this handbook that are critical to ensuring that risk evaluations are consistent with the science standards in the LCSA. These recommendations are provided in Appendix D³, PSURY L Q J⁴ 5 LVN⁵ & K ACC documents that each of these key aspects, which have been unchanged since 2000, be incorporated into the risk evaluation rulemaking.

d. Clearly Addressing Variability and Uncertainty

Section 26(h)(4) calls out the importance of clarity and transparency, particularly as it relates to characterizing variability and uncertainty in both the methods and protocols as well as the models and the information.³⁹ EPA must not underestimate the importance of clarity and full transparency when describing this information as it should be a critical consideration when contemplating potential risk management actions. Where feasible, to be consistent with Sections 6 and 26, EPA must characterize uncertainty and variability quantitatively, particularly for the refined risk evaluations. This is fully consistent with a fit-for-purpose approach to risk evaluation. Any limitations in the analysis must be explained clearly, including discussion of the impacts that the limitations may have on the end results. For refined risk evaluations, EPA must ensure that when a quantitative uncertainty analysis is provided, it must be probabilistic and the data, methods, and models used are described sufficiently to allow for independent re-analysis.⁴⁰ If a quantitative uncertainty analysis is not provided, the omission should be justified and included in the risk evaluation.⁴¹ Equally important, EPA must ensure that variability in effects or responses across relevant populations(s) are discussed with significant uncertainties noted.⁴²

, Q⁴³ 4⁴⁴ !! ¶⁴⁵ 7⁴⁶ 8⁴⁷ 9⁴⁸ \$ & & ¶⁴⁹ V⁵⁰ & H Q W H U⁵¹ I R U⁵² \$ G Y D Q F L Q J⁵³ 5 LVN⁵⁴ \$ V V H V V P H Q W⁵⁵ 6⁵⁶
invited participant workshop to explore approaches to improve methods for presenting uncertainty

³⁷ 6 H F W L R Q⁵⁷ 4⁵⁸ 5⁵⁹ K⁶⁰ 6⁶¹ 7⁶² 8⁶³ 9⁶⁴ V W D W H V⁶⁵ W K D W⁶⁶ W K D W⁶⁷ W K D W⁶⁸ W K D W⁶⁹ W K D W⁷⁰ W K D W⁷¹ W K D W⁷² W K D W⁷³ W K D W⁷⁴ W K D W⁷⁵ W K D W⁷⁶ W K D W⁷⁷ W K D W⁷⁸ W K D W⁷⁹ W K D W⁸⁰ W K D W⁸¹ W K D W⁸² W K D W⁸³ W K D W⁸⁴ W K D W⁸⁵ W K D W⁸⁶ W K D W⁸⁷ W K D W⁸⁸ W K D W⁸⁹ W K D W⁹⁰ W K D W⁹¹ W K D W⁹² W K D W⁹³ W K D W⁹⁴ W K D W⁹⁵ W K D W⁹⁶ W K D W⁹⁷ W K D W⁹⁸ W K D W⁹⁹ W K D W¹⁰⁰ W K D W¹⁰¹ W K D W¹⁰² W K D W¹⁰³ W K D W¹⁰⁴ W K D W¹⁰⁵ W K D W¹⁰⁶ W K D W¹⁰⁷ W K D W¹⁰⁸ W K D W¹⁰⁹ W K D W¹¹⁰ W K D W¹¹¹ W K D W¹¹² W K D W¹¹³ W K D W¹¹⁴ W K D W¹¹⁵ W K D W¹¹⁶ W K D W¹¹⁷ W K D W¹¹⁸ W K D W¹¹⁹ W K D W¹²⁰ W K D W¹²¹ W K D W¹²² W K D W¹²³ W K D W¹²⁴ W K D W¹²⁵ W K D W¹²⁶ W K D W¹²⁷ W K D W¹²⁸ W K D W¹²⁹ W K D W¹³⁰ W K D W¹³¹ W K D W¹³² W K D W¹³³ W K D W¹³⁴ W K D W¹³⁵ W K D W¹³⁶ W K D W¹³⁷ W K D W¹³⁸ W K D W¹³⁹ W K D W¹⁴⁰ W K D W¹⁴¹ W K D W¹⁴² W K D W¹⁴³ W K D W¹⁴⁴ W K D W¹⁴⁵ W K D W¹⁴⁶ W K D W¹⁴⁷ W K D W¹⁴⁸ W K D W¹⁴⁹ W K D W¹⁵⁰ W K D W¹⁵¹ W K D W¹⁵² W K D W¹⁵³ W K D 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and risk information in federal chemical hazard assessment programs. Participants included more than 60 experts in toxicology, risk assessment, risk communication, exposure assessment, and hazard characterization drawn from academia, government (including EPA), and industry, and non-governmental organizations. ACC encourages EPA to consider the 2016 publication⁴³ that resulted from this workshop to inform improved methods for presenting uncertainty information as it relates to hazard assessment, a critical element of the risk evaluation process.

e. **Ensuring Appropriate Peer Review and Forming a Science Advisory Committee on Chemicals**

Section 26(h)(5) recognizes the important role of peer review.⁴⁴ &RQVLVWHQW^L ZLWK^L (3\$¶V^L Review Handbook,⁴⁵ the most robust reviews should be reserved for the refined risk evaluations. ACC expects that EPA will adhere to the principles, guidance and criteria set forth in the OMB Information Quality Bulletin for Peer Review,⁴⁶ which EPA has incorporated and expanded upon in its Peer Review Handbook. For consistency with this requirement of the LCSA, ACC recommends that the specific peer review process that will be used for refined risk evaluations be clearly described in the risk evaluation rulemaking. This includes elements relating to how reviewers will be selected, transparency of the review process, inclusion of stakeholders and the need for a robust consensus report. As depicted in Figure 1, a robust peer review should be conducted on the draft refined risk evaluation.⁴⁷ Robust peer review and public comment will serve to improve the quality, credibility, and acceptance of the final risk evaluation. Appendix E³ (QVXULQJ^L 5REXVW^L provides specific recommendations for incorporation into the rulemaking.

ACC also recommends, consistent with Section 26(o) of the LCSA, that EPA expeditiously form a Science Advisory Committee on Chemicals (SACC) and use this group (or a subgroup of this group) WR^L FRQGXFW^L WKH^L SHHU^L UHYLHZ^L RI^L UHQHCHULVS^L DOXDWLR^L Advisory Committee does not meet the requirements of the LCSA nor is the membership of the committee sufficient to ensure high quality reviews, as ACC has commented in the past.⁴⁸

⁴³ Beck NB, et al., Approaches for describing and communicating overall uncertainty in toxicity characterizations: U.S. Environmental Protection Agency's Integrated Risk Information System (IRIS) as a case study; Environ Int. 2016, available at: <http://www.sciencedirect.com/science/article/pii/S0160412015301367>.

⁴⁴ Section 26(h)(5) states that the Administrator shall ensure independent verification or peer review of the information or of the procedures, measures, methods, protocols, methodologies, or models.

⁴⁵ EPA, Peer Review Handbook, 2015, available at: https://www.epa.gov/sites/production/files/2016-03/documents/epa_peer_review_handbook_4th_edition.pdf.

⁴⁶ OMB, Peer Review Bulletin, 2005, available at: https://www.whitehouse.gov/sites/default/files/omb/assets/omb/fedreg/2005/011405_peer.pdf.

⁴⁷ Some of the refined risk evaluations may lead to costly risk management measures and will thus need to be treated as influential or highly influential scientific assessments.

⁴⁸ See ACC comments available at: <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2015-0805-0012>.

VIII. The Proposed Rule Should Implement a Weight of the Scientific Evidence Approach (WoE)

Section 26(i) of the LCSA requires EPA to make decisions using a WoE approach.⁴⁹ While many groups have described and discussed what is meant by a WoE approach,⁵⁰ the June 7, 2016, Congressional Record provides a very clear definition.⁵¹ This definition, added by senators, is fully consistent with the definition provided by the House of Representatives.⁵² ACC recommends that, to ensure clarity and consistency in applications, the definition from the Congressional Record be added to the risk evaluation rulemaking as follows: “WKH^L WHUP^L μ ZHL J KW^L RI^L HYLGHQFH ¶^L UHIHUV^L WR^L Establish^L KWHPDWLF^L protocol to comprehensively, objectively, transparently, and consistently, identify and evaluate each stream of evidence, including strengths, limitations, and relevance of each study and to integrate evidence as necessary and appropriate based upon strengths, limitations, and relevance.”

This definition is meant to apply to human and environmental/ecological risk evaluations and should be applied in a fit-for-purpose manner to both screening and refined risk evaluations. As refined risk evaluations must be rigorous to inform potential risk management activities, the WoE standard becomes even more important in this context. However, for all types of risk evaluations, a WoE approach will increase reliability, transparency, clarity, and consistency.

The best available science provision at Section 26(h) also applies to both the Section 6(b)(4)(F)(v) and 26(i) WoE requirements, such that the WoE review itself must be based on best available evidence. The rulemaking should make this clear. It should also clearly differentiate between WoE and SoE review, and explain why a SoE review does not meet either the best available evidence or the WoE requirements of the statute.

a. Systematic Review is Required

Consistent with the definition of WoE, a systematic review is required. This means EPA must, among other steps, provide clear criteria for judging the quality and relevance of all evidence and must then integrate all the evidence based on the identified strengths and limitations and relevance. Systematic review is rigorous. However, once in place, and once the criteria and quality standards are identified and the approach is outlined, the rigor, clarity, and transparency of EPA assessments over time will be greatly improved. There will be tremendous cost, effort, and time savings once fully implemented.

ACC recommends that EPA follow the standards for systematic review defined by the Institute of Medicine (IOM).⁵³ The IOM report provides a clear discussion of what is required for a systematic

⁴⁹ 6HFWLRQ^L ± † σ The Administrator shall make decisions under sections 4, 5, and 6 based on the weight of the scientific evidence.”

⁵⁰ See for example Lutter, R et al., Improving weight of evidence approaches to chemical evaluations; Risk Anal. 2015 Feb; 35(2):186-92. Available at: <http://onlinelibrary.wiley.com/doi/10.1111/risa.12277/full>.

⁵¹ See Senate Congressional Record, June 7, 2016 at page S3518, available at: <https://www.congress.gov/crec/2016/06/07/CREC-2016-06-07-pt1-PgS3511.pdf>.

⁵² See House of Representatives Report 114-175 at page 33, available at: <https://www.congress.gov/114/crpt/hrpt176/CRPT-114hrpt176.pdf>.

⁵³ Institute of Medicine (IOM), Finding what works in Health Care: Standards for Systematic Review, 2011, available at: <http://www.nationalacademies.org/hmd/Reports/2011/Finding-What-Works-in-Health-Care-Standards-for-Systematic-Reviews.aspx>.

review and this approach should be incorporated into the risk evaluation rulemaking. Key elements of a systematic review, which have not changed over time, should include:

i. Development of a Protocol

The protocol, developed before the risk evaluation begins, defines the methodologies that will be used in the assessment. It is made publicly available before the assessment begins and becomes a living document that can be commented upon and modified as needed. The protocol, arguably the most important part of a systematic review includes: a clear testable question/hypothesis, the planned search strategy (including criteria for inclusion and exclusion of studies), the criteria that will be used for study quality and risk of bias evaluations (including for example consideration of study design and confounders), the plan for integrating/synthesizing evidence using a WoE approach, the plan for dose-response analysis (if necessary), the plan for quantifying and presenting risk findings, and the plan for peer review of the assessment.⁵⁴

ii. Search Strategy

The search strategy (including predefined study inclusion/exclusion criteria, literature sources, search terms, and outreach plan for obtaining stakeholder data) used to identify relevant literature (both negative and positive studies) is well documented and is made available to the public. Any restrictions placed on the literature search or data access are noted and explained.⁵⁵

iii. Transparency

Sufficient data for the critical studies and the models used in the assessment are available to interested external parties so as to enable them to replicate/verify the assessment outcomes and to judge the scientific credibility of the data/models. Confidential business information (CBI) is protected.⁵⁶

b. A Systematic Review is Not Automatically a WoE Assessment

The definition of WoE requires that a systematic review approach be used. A systematic review approach is defined as a process that is well documented, transparent, and reproducible. The systematic review protocol will define, in advance of conducting the evaluation, the quality criteria and the approach that EPA will use. Unfortunately, the term 'systematic review' is often loosely used and many scientists often confuse a systematic literature review with the conduct of a full

⁵⁴ Finding what works in Health Care: standards for Systematic Review, 2011, available at: <http://www.nap.edu/catalog/13059/finding-what-works-in-health-care-standards-for-systematic-reviews>; NAS Review of EPA's Integrated Risk Information System (IRIS) Process, 2014, available at: <http://www.nap.edu/catalog/18764/review-of-epas-integrated-risk-information-system-iris-process>; OHAT systematic review handbook, available at <https://ntp.niehs.nih.gov/pubhealth/hat/noms/index-2.html>; and EFSA Application of Systematic review, available at: <http://www.efsa.europa.eu/en/efsajournal/pub/1637>.

⁵⁵ Ibid; Fenner-Crisp and Dellarco, 2016.

⁵⁶ National Research Council, National Academy of Sciences, Models in Environmental Regulatory Decision Making, 2007, available at: <http://www.nap.edu/catalog/11972/models-in-environmental-regulatory-decision-making>; Fenner-Crisp and Dellarco, 2016.

systematic review. A systematic review requires not only a plan for systematically reviewing the literature, but also requires that plans for analysis and data integration be included in the protocol.

However, the systematic review process itself does not automatically dictate the approach for analysis and evidence integration. Many systematic reviews, as will be described below, do not necessarily conduct evaluations using a weight of evidence framework for integrating studies based on their strengths, limitations and relevance. This distinction is critically important. EPA, and stakeholders, must be cautious to not conflate WoE and systematic review. The LCSA requires both a systematic review approach and a WoE approach. While both are required, they are separable and the terms should not be confused. The WoE approach mandated by the LCSA is very specific to how EPA will not only weigh information, but how that information should be integrated. This integration step is critically important.

c. WoE and Systematic Review for Screening Level Risk Evaluations

While it may appear overly rigorous on first glance, both WoE and systematic review approaches can be applied to screening level risk evaluations. This approach is consistent with the approach taken by ECHA where the WoE evaluation is influenced by the amount of information needed and the importance of the decision being taken, as well as the consequences of the decision.⁵⁷

In screening level evaluations, EPA should use the best available data, based on its strengths, limitations and relevance, as is appropriate (fit-for-purpose) for a screening level evaluation. The protocol for a screening level evaluation should clearly articulate the screening tools, models, data and information that will be used in the evaluation, and should also describe how all the information will be integrated, based on the strengths, limitations and relevance of the data. The systematic review approach will ensure clarity and transparency in the conduct of the screening level evaluations and the WoE approach will ensure that the best screening tools and information are given the most weight. This will ensure that EPA is using the best available science for the screening level evaluations.

d. WoE and Systematic Review for Refined Risk Evaluations

Similar to the approach described above, both WoE and systematic review approaches must be applied to refined risk evaluations. The key difference will likely be that there exists more data and information, more data streams to evaluate (including mechanistic and mode of action (MOA) information, and more complex considerations of both dose and human relevance, in addition to evaluating study quality and relevance. As these evaluations may inform risk management actions, it is critically important that they are also transparent, reproducible, and rely upon the best available science. Many publications describe tools that exist to evaluate the quality of data, including mechanistic data,⁵⁸ and provide examples of approaches to integrate the data using a WoE approach.⁵⁹

⁵⁷ ECHA, Practical guide How to use alternatives to animal testing to fulfil your information requirements for REACH registration, Version 2.0, 2016, available at:

https://echa.europa.eu/documents/10162/13655/practical_guide_how_to_use_alternatives_en.pdf.

⁵⁸ See for example Lynch H., et al., Systematic Comparison of Study Quality Criteria, Regul Toxicol Pharmacol, 2016, available at: <http://www.sciencedirect.com/science/article/pii/S0273230015301525>; Greene et al., Challenges in Developing a

While the LCSA requires EPA to conduct both WoE and systematic reviews, ACC recognizes that while what constitutes a high quality WoE review and a systematic review will not change over time, the approach EPA take may take will likely continue to evolve. ACC encourages EPA to fully engage all stakeholders in the continued development of these approaches.

e. Strength of Evidence is Not the Same as WoE

A strength of evidence (SoE) approach should not be confused with a WoE approach. Similarly, programs that use SoE approaches should not be considered equivalent to programs that use a WoE approach. EPA should not rely on data from these programs as they do not meet the requirements of the LCSA.

SoE is simply not as robust as WoE. Typically SoE approaches have emphasized one or a few studies that report an association between a chemical and a health effect regardless of their quality, replicability, or consistency, and often fail to integrate data gathered from a variety of sources. SoE studies also often ignore negative data. The Office of Health Assessment and Translation (OHAT) at NIEHS conducts systematic reviews and considers the risk of bias of individual studies. However, OHAT does not rely on these findings during integration and OHAT does not conduct a full evaluation of the quality of each individual study. Risk of bias is only a small piece of a full quality evaluation. Similarly concerning, OHAT examines only at the strength of the body of evidence, ignoring the strength of individual studies. Unfortunately, this SoE approach allows OHAT to reach flawed conclusions, e.g., that a body of sub-par studies provides the same level of rigor as a high quality study. This approach is not scientifically defensible. In addition, the OHAT process omits important middle steps relevant to causal inference. The International Agency for Research on Cancer (IARC) also uses a SoE approach, giving more weight to positive studies than negative studies and often paying less attention to the quality and relevance of those individual studies. EPA must employ the Congressionally-mandated WoE approach, not a SoE approach.

In implementing the Hazard Communication Standard (HCS), OSHA made clear there are differences between SoE and WoE, acknowledging that WoE goes beyond SoE. In discussing FDUFLQR JHQLFLW \ \ 26 + \$ VWDWHG W KDW :R(3 LQYROYHM WKH FRQ strength of evidence, that influence the likelihood that a chemical may pose a carcinogenic hazard, such as tumor type and background incidence, multisite responses, mode of action, and the comparison of absorption, distribution, metabolism and excretion between test animals and

Systematic Review Protocol for Environmental Contaminants In: The Toxicologist: Supplement to Toxicological Sciences, 150 (1), Society of Toxicology, 2016. Abstract no. 2166, available at: <https://www.toxicology.org/pubs/docs/Tox/2016Tox.pdf>.

⁵⁹ See for example Lavelle K, et al., Framework for Integrating Human and Animal Data in Chemical Risk Assessment, Regul Toxicol Pharmacol, 2012, available at: <http://www.sciencedirect.com/science/article/pii/S0273230011002029>; Adami HO et al., Toxicology and epidemiology: improving the science with a framework for combining toxicological and epidemiological evidence to establish causal inference. Toxicol Sci., 2011, available at: <http://toxsci.oxfordjournals.org/content/122/2/223.long>; Goodman JE., Weight-of-evidence evaluation of short-term ozone exposure and cardiovascular effects. Crit Rev Toxicol., 2014, available at: <http://www.tandfonline.com/doi/abs/10.3109/10408444.2014.937854?journalCode=itxc20>; Lutter, R et al., Improving weight of evidence approaches to chemical evaluations; Risk Anal., 2015, available at: <http://onlinelibrary.wiley.com/wol1/doi/10.1111/risa.12277/full>.

A related issue concerns health and safety studies sponsored by companies that are not in the public domain. Some companies will have concerns that certain health and safety studies they have funded will be made public by EPA and then widely available to others who did not make any financial contribution or provide data compensation to the data owner. ACC urges EPA to work with companies to enable them to share studies with the Agency without losing their right to fair and equitable data compensation. EPA should consider making a robust study summary publicly available rather than the full study in such circumstances. If other scientists interested in the actual studies come forward to verify the data and/or quality of the study, etc., those interested scientists should be required to sign a non-disclosure agreement prohibiting personal use of the study for any other purpose.

XI. EPA Should Utilize Fit-for-Purpose Exposure Evaluation Tools

Recognizing that measured exposure information that is representative, reproducible and reliable is frequently unavailable, EPA will need high quality, fit-for-purpose exposure models to inform both scoping and refined risk evaluations. Many exposure models/tools exist to inform scoping/screening to allow EPA to distinguish uses that present no concern from those that require a targeted higher tier assessment.

Consistent with Section 26, models must be used in a manner consistent with the intended use of the information. Lower tier, very conservative models that are useful for scoping and screening will not be sufficient for the refined risk evaluations necessary to inform risk management decisions. For refined evaluations, EPA should use higher tier exposure tools and refined information, preferably measured data when it exists and is reliable.

In addition to EPA, the OECD recommends that EPA explore the exposure models used in Europe by ECHA, EU member states, and REACH registrants. These tools have been widely used throughout the European Union. Tables 1 and 2 below identify some of the tools available to EPA. Further details on exposure tools are provided in Appendix F.

Table 1. EPA Toolbox of Exposure Models⁶²

| Screening Assessment Tools | | | Refined Assessment Tools | | |
|----------------------------|------------------|-----------------------------|-------------------------------|-------------------------------|-----------------|
| <i>Environmental</i> | <i>Worker</i> | <i>Consumer</i> | <i>Environmental</i> | <i>Worker</i> | <i>Consumer</i> |
| Chemsteer (v3.0) | Chemsteer (v3.0) | E-Fast (v2014) | Chemsteer ⁺ (v3.0) | Chemsteer ⁺ (v3.0) | MCCEM (v2.2) |
| E-Fast (v2014) | | CEM beta (1.3) [*] | E-Fast ⁺ (v2014) | | WPEM (v3.2) |
| EPI Suite (v411) | | Sheds-HT beta [*] | | | AMEM (1990) |

^{*}denotes models for which validation is not yet complete

⁺denotes models for which data can replace defaults to refine the assessment

⁶² EPA exposure models from <https://www.epa.gov/tsca-screening-tools>.

Table 2. REACH Toolbox of Exposure Models

| Screening Assessment Tools | | | Refined Assessment Tools | | |
|----------------------------|-------------------|-------------------|--------------------------|---------------------|-----------------|
| <i>Environmental</i> | <i>Worker</i> | <i>Consumer</i> | <i>Environmental</i> | <i>Worker</i> | <i>Consumer</i> |
| CHESAR (v3.0) | CHESAR (v3.0) | CHESAR (v3.0) | CHESAR (v3.0)* | ART (v1.5) | EGRET (v2) |
| ECETOC TRA (v3.1) | ECETOC TRA (v3.1) | ECETOC TRA (v3.1) | ECETOC TRA (v3.1)* | PEST | REACT (2009) |
| PetroRisk | BAMA/FEA | BAMA/FEA | | Stoffenmanager (v6) | ConsExpo (v4.1) |

* denotes models for which data can replace defaults to refine the assessment

The REACH exposure toolbox includes the Chemical Safety Assessment and Reporting Tool (CHESAR), which incorporates the ECETOC Targeted Risk Assessment (TRA) component for scoping and screening exposures to workers, general population, consumers and the environment. The REACH toolbox also includes BAMA for evaluating aerosol products in indoor environments, and PetroRisk for the evaluation of petroleum products.

The TRA tool allows risk evaluation practitioners to conduct a screening level assessment of exposures to workers, consumers, and the environment, all in the same model. Reliable regulatory decision making using a minimum amount of data, at the screening level, is simplified with the TRA. Risks can be assessed in a tiered, integrated approach and communicated in a manner that is relevant and understandable. We encourage EPA to explore the use of this tool, and similar tools to help ensure the efficient, timely, and high quality implementation of the LCSA. Appendix G provides further details on the TRA tool.

The toolbox also includes higher tier models like EGRET for solvents, REACT for cleaning products, PEST for plastic additives, ConsExpo for consumer products as other products. For more refined work place exposure, the toolbox includes Stoffenmanager and ART. These REACH models are publicly available and well documented.⁶³ They have been extensively reviewed in ECHA-led conferences, science advisory panels, scientific journals, and many other fora. Importantly, they have been utilized for the registration of over 10,000 substances, establishing their strong track record. ACC encourages EPA to explore the further use of these widely available modeling tools.

XII. The Requirements of Sections 6 and 26 Apply to Environmental Risk Evaluations

Under the LCSA, EPA will continue to have an obligation to protect the environment. Setting aside the clearly human health specific comments, the framework and methodologies described in these comments can generally apply to both human health and environmental risks. There are certain considerations specific to environmental risk evaluation that merit further discussion.

As with human health evaluations, there is an opportunity to improve environmental risk evaluations, and sections 6 and 26 of the LCSA require high quality information and science standards be met. An

⁶³ See for example ECHA Guidance on information requirements and Chemical Safety Assessment Chapter R.16: Environmental exposure assessment Version 3.0, 2016, available at https://echa.europa.eu/documents/10162/13632/information_requirements_r16_en.pdf.

unreasonable risk determination must be based on hazard and exposure-- it cannot be triggered by volume alone and/or intrinsic properties without assessing behavior in the environment.

In a tiered testing paradigm, we suggest that EPA prefer high quality testing data. When not available, EPA should rely on category approaches/ analogues & read-across, and QSAR models. EPA should have a transparent approach for evaluating endpoints/data in each of these categories. Industry scientists often have knowledge of risk assessment processes globally, including an understanding of potential environmental impacts. ACC encourages EPA to leverage this knowledge and engage early and frequently with industry throughout the risk evaluation process.

a. Advancing Models for Environmental Risks

Environmental risk evaluation would be greatly improved if there were a larger suite of models that EPA found acceptable. There are many hazard prediction models available of varying quality and utility. Models tailored for specific categories of chemicals may give a more accurate output than more generic models. As such, it would be helpful for EPA to allow a greater range of tailored and externally sourced models into the risk evaluation process, provided the models undergo an assessment for acceptability.

ACC would like to work with EPA to develop a more transparent set of acceptance criteria for environmental models. This would permit and accelerate the acceptance of existing and externally sourced models for use in risk evaluation. Stakeholders would benefit from a better understanding of the criteria EPA uses to validate new models, so that users can participate in the acceptance process or eliminate models that are inappropriate. In addition, new models including those specific for certain chemical families could be constructed in accordance with these criteria. These criteria could also be used to generate a running list of pre-approved models. Such a list would provide a degree of flexibility and reliability that will lead to timely and improved risk evaluations. ACC would welcome the opportunity to begin a dialogue with EPA to work together to develop these important criteria for model acceptance.

b. Improving Data Sourcing, Generation, and Evaluation

There is a wealth of environmental testing data available in REACH. ACC encourages EPA to continue to work with ECHA, OECD, ECETOC, and other stakeholders to move towards standardization of data for the global evaluation and acceptance of environmental studies. Through REACH, the Klimisch approach has become a widely accepted tool for evaluating the quality of data. More recently, a tool specific for ecotoxicity data, the criteria for reporting and evaluating ecotoxicity data (CRED) has been proposed.⁶⁴ ACC encourages EPA to adopt an approach such as this through a transparent process that engages all stakeholders in the process.

⁶⁴ Moerland, CT. et al., CRED: Criteria for reporting and evaluating ecotoxicity data, Environ Toxicol Chem., 2016, available at: <http://onlinelibrary.wiley.com/doi/10.1002/etc.3259/abstract>.

ACC also encourages EPA to revisit the state of the science regarding difficult to test substances to allow for the flexibility to provide data that takes the intrinsic properties of the substance into consideration. A better articulation by EPA of the criteria for acceptance of alternative methods for poorly-soluble, difficult to test substances would be extremely helpful and we encourage EPA to look to OECD guidance.⁶⁵

For instance, the use of activity to describe the degree of saturation achieved by a compound in a given media is particularly useful for poorly soluble lipophilic substances that display a narcosis mode-of-action in aquatic organisms. ACC recommends that EPA find this approach acceptable. In addition to this approach, chemical activities may provide valuable estimates of the proximity of measured concentrations to potentially toxic levels. These values are easy to calculate and allow the comparison of concentration data in various matrices that are of differing units. Finally, ACC encourages EPA to adopt new analytical approaches, for polymers and UVCBs, regarding water solubility. ACC members have a wealth of expertise in this space, including experiences from working with Canadian and Korean governments. ACC would welcome the opportunity to discuss these approaches with EPA.

c. **Persistent, Bioaccumulative and Toxic (PBT) Substances**

PBT substances are substances that resist degradation in the environment and in organisms, leading to progressively higher and unpredictable concentrations in a food web and therefore may pose risks to top predators and humans. When assessing a substance for potential PBT properties, EPA must go beyond the numerical screening criteria used today that screen only for the potential to behave as PBTs in the environment. Recent publications have discussed this approach in the context of PBTs.⁶⁶ Relevant reliable data should not be excluded simply because screening criteria are met. For example, a bioconcentration factor may indicate that a substance could bioconcentrate in a fish but if the substance is not found in water, cannot reach levels in the fish that can cause toxicity and will not biomagnify in food webs due to metabolism. All of this data should be used to assess if that substance is actually bioaccumulative in the environment. In addition to using all data to assess these endpoints, it is important to evaluate each study for its quality and relevance to the endpoint being assessed, taking into consideration the physical chemical properties of the substance.

XIII. EPA Should Leverage International and Inter-Agency Cooperation

Section X, above, discusses the need for EPA to ensure that information from other offices within EPA is considered to inform risk evaluations. However, the universe from which EPA could obtain useful information is much larger. EPA should leverage data and information reasonably available from other jurisdictions where that data and information has applicability in the United States and is of sufficient

⁶⁵ See for example OECD Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures, available at: http://www.oecd-ilibrary.org/environment/guidance-document-on-aquatic-toxicity-testing-of-difficult-substances-and-mixtures_9789264078406-en.

⁶⁶ See for example, The Origin and Evolution of Assessment Criteria for Persistent, Bioaccumulative and Toxic (PBT) chemicals and Persistent Organic Pollutants (POPs), M. Matthies et al, Environ. Sci.: Processes Impacts, 2016, DOI 10.1039/C6EM00311G, and Comparing Laboratory and Field Measured Bioaccumulation Endpoints, Burkhard et al, IEAM, Vol 8, Number 1, 2011.

scientific quality to meet the science standards required under the LCSA. For example, there is a significant amount of information available, including robust study summaries, associated with submissions to ECHA for REACH chemical evaluations.⁶⁷ In addition, (3\$ ¶ V^L Z RUN^L Z LWK^L & D Q DGD the Regulatory Cooperation Council (RCC) has provided EPA with data and information relevant to VHYHUDO^L FDVH^L VWXGLHV^L RQ^L FK HPLFDV^L WKDW^L DUH^L RQ^L (3\$ ¶ V^L ± !! ¶ |^L 8S learnings from that work should be leveraged by EPA in its risk evaluation work under the LCSA.

Similarly, EPA should not be compelled to further evaluate a chemical and its conditions of use if another regulatory authority (either in the US or elsewhere) has already conducted an evaluation, provided the uses and exposures are comparable to those in the United States and the quality of the evaluation meets the scientific standards required under the LCSA.

EPA has relied on assessments completed by other jurisdictions and agencies in the past and there is no reason it should not continue to do so in appropriate circumstances where the scientific quality meets the VWDQGDUGV^L GLFWDWHG^L E \^L WKH^L /&6\$^L DQG^L FRQGLWLRQV^L RI^L XVH^L DUH^L UHO minimum, EPA should coordinate with other federal agencies with similar/sometimes overlapping/relevant jurisdictions as contemplated by Section 9 of the LCSA.

XIV. Incorporating High Throughput Tools and Alternative Methods

To improve efficiency, particularly for screening level risk evaluations, EPA will need to adopt alternative methods that allow for the evaluation of chemicals that may not have robust testing data available. Read Across and QSAR modeling are important toxicological tools that can be used to assess hazards and risks of a substance without conducting additional animal toxicity tests.⁶⁸ Read Across uses relevant information from analogous substances to predict a specific toxicity endpoint for the target substance.⁶⁹ EPA, OECD and industry have gained considerable experience using read across approaches under both (3\$ ¶ V^L + 39^L & KDOOHQ J H^L 3UR J UDP^L DQG^L WKH^L 2(&'^L &RRSHUDWL YH^L & K HPLFD minimum, EPA and OECD have issued guidance on methods for forming categories for use in read across.⁷⁰ More recently, ECHA has developed the Read Across Assessment Framework (RAAF) which should also be considered by OPPT.⁷¹

⁶⁷ Non-confidential REACH data is made easily available through AMBIT, which can be accessed at: http://cefic-lri.org/lri_toolbox/ambit/.

⁶⁸ See for instance <http://ehp.niehs.nih.gov/1104666/> and https://echa.europa.eu/documents/10162/13655/pg_avoid_animal_testing_en.pdf.

⁶⁹ Patlewicz et al., Read-Across Approaches ± Misconceptions, Promises and Challenges Ahead, 2014, available at http://altweb.jhsph.edu/altex/31_4/FFTPatlewicz.pdf (5 HDG^L \$FURVV^L IURP^L \$QDOR 5VID&DDHURVHVLV^L D^L WHI ILOOLQ J^L GDWD^L JDSV^L 7R^L μ UHDG^L DFURVV^L ¶^L LV^L WR^L DSSO \^L GDWDOR 5VID&DDHURVHVLV^L D^L WHI toxicity, etc.) to a similar untested chemical. The read across technique is often applied within groups of similar chemicals assembled for assessment using either analog approach (grouping based on a very limited number of chemicals) or category approach (grouping based on a larger number of chemicals). In an analog/ category approach, not every chemical needs to be WHVWHG^L IRU^L HYHU \^L HQGSRLQW^L □

⁷⁰ See EPA, Development of Chemical Categories in the HPV Challenge Program, available at: <https://web.archive.org/web/20080829212006/http://www.epa.gov/chemrtk/pubs/general/categuid.htm>; OECD, Guidance on Grouping of Chemicals, Second Edition, available at:

[http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono\(2014\)4&doclanguage=en](http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2014)4&doclanguage=en)

⁷¹ See https://echa.europa.eu/documents/10162/13628/raaf_en.pdf.

Historically, Read Across has relied upon traditional toxicity datasets; however, advanced approaches for biological profiling, such as high throughput screening and high content profiling, hold considerable promise for improving the scientific basis for developing categories, analyzing analogues and supporting quantitative (e.g., relative potency) Read Across.⁷²

can also be used to

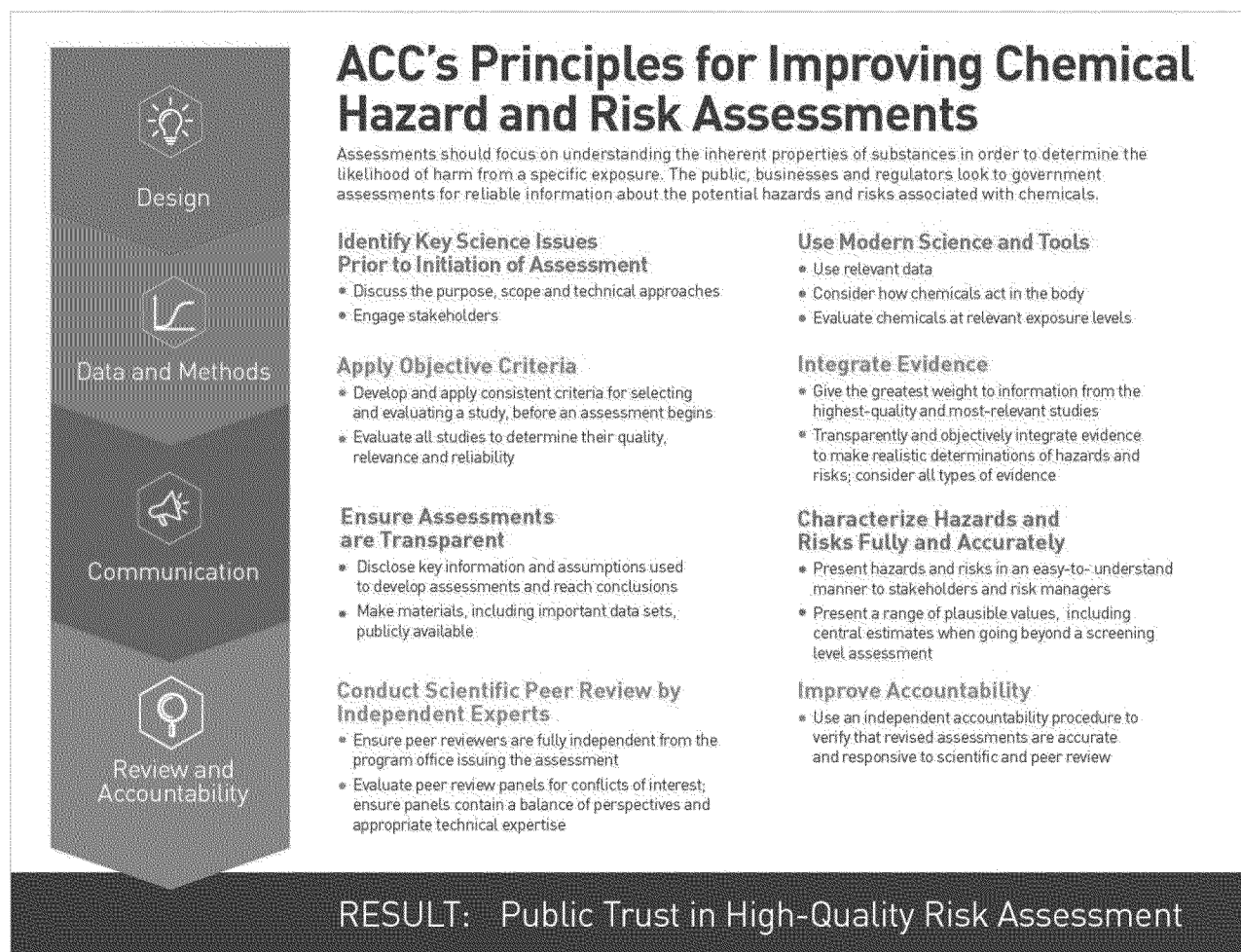
advanced

biological profiling technologies for use in Read Across,

XV. Stakeholders and EPA Must Be Held to the Same High Standard

Sections 6 and 26 set high quality standards for the conduct of risk evaluations that must be incorporated into the evaluation program for decades to come. We recommend that these same high quality standards be incorporated into the guidance for stakeholders to inform the submission of draft risk evaluations which shall be considered by the Administrator as required in Section 26(l)(5). The high quality standards required by the LCSA should apply to everyone. The new statute demands it and ACC and its member companies stand ready to be held to these same high quality standards.

⁷² See for example <http://www.ncbi.nlm.nih.gov/pubmed/27026708>.



Appendix B: Improving Hazard Assessment

ACC recommends that these important steps in a hazard assessment be incorporated into EPA's rulemaking for risk evaluation. This will ensure that the conduct/process of developing refined risk evaluations is consistent with the high quality demanded by Sections 6 and 26 of the LCSA.

Critical Steps for Hazard Assessment:

1. A pre-defined established weight-of-evidence approach, addressing causal relationships, is applied in a systematic manner to integrate, weigh the lines of relevant evidence, and effectively use all relevant information. This includes ensuring that both positive and negative studies are weighed objectively and that the highest quality and most relevant studies are given the most weight/consideration. Judgments and choices should all be transparently presented. A "strength of evidence" approach is not acceptable.⁷³ Section VIII of these comments discusses the weight of evidence (WoE) concept in more detail.
2. EPA should include a robust discussion of key lines of evidence and inherent uncertainties, alternative interpretations, other issues that may have prompted debate, and how these issues are addressed.⁷⁴
3. EPA should identify, explain, and discuss the level of adversity of the chosen endpoint(s).⁷⁵
4. Biologically plausible mode of action (MoA) information should be considered and fully incorporated. The MoA analysis should include a consideration of category analogs as a complement to chemical specific data, and existing knowledge must be leveraged on already established MoAs similar to the substance of interest.⁷⁶
5. EPA should provide a discussion of whether the key events within the MoA would progress to an adverse effect relative to concentration/dose and anticipated human exposure (duration/magnitude/route), and life stage.⁷⁷

⁷³ NAS, 2014 ; Fenner-Crisp and Dellarco, 2016.

⁷⁴ Ibid.

⁷⁵ EPA, Risk Assessment for Noncancer Effects, available at: <https://www.epa.gov/fera/risk-assessment-noncancer-effects>; EPA, A Review of the Reference Dose and Reference Concentration Processes, 2002, available at: <https://www.epa.gov/sites/production/files/2014-12/documents/rfd-final.pdf>.

⁷⁶ EPA, Guidelines for Carcinogen Risk Assessment, 2005, available at: https://www3.epa.gov/airtoxics/cancer_guidelines_final_3-25-05.pdf; Fenner-Crisp and Dellarco, 2016.

⁷⁷ EPA Guidelines for Carcinogen Risk Assessment, 2005; IPCS Mode of Action/Human Relevance Framework, available at: <http://www.who.int/ipcs/methods/harmonization/areas/cancer/en/>; Fenner-Crisp and Dellarco, 2016.

Appendix C: Improving Dose Response Assessment

ACC recommends that these important steps in a dose response assessment be incorporated into EPA's rulemaking for risk evaluation. This will ensure that the conduct/process of developing refined risk evaluations is consistent with the high quality demanded by Sections 6 and 26 of the LCSA.

Critical Steps for Dose Response Assessment:

1. The dose responses should be plotted for all relevant non-cancer endpoints of concern and a distribution of hazard values or points of departure (POD) should be provided for all relevant endpoints. The selection of the hazard values must be well justified and supported by the overall database.⁷⁸
2. When biologically plausible, potential carcinogenic effects should be modeled and presented using non-linear approaches in addition to linear modeling approaches.⁷⁹
3. A non-linear, point of departure modeling approach should be used for non-genotoxic carcinogens. For genotoxic carcinogens acting through MOAs that are clearly understood to be threshold events (e.g., clastogenesis induced by DNA-DNA and/or DNA-protein crosslinks such as binding to spindle apparatus), a non-linear model should be used.⁸⁰
4. EPA must take into consideration natural background levels as well as endogenous human production of compounds when evaluating dose-response. Hazard values below background should not drive risk management determinations.⁸¹
5. The endpoints used in the dose-response assessment should be those associated with adverse responses in humans, biologically plausible in humans, and derived from studies of high quality and relevance. Bradford Hill Considerations should be used to evaluate critical endpoints.⁸²
6. The nature of responses (e.g., biochemical, morphological, physiological or functional change, severity of the effect, reversibility) and their dose-responses (e.g., steepness or shallowness of dose-response curve, dose spacing between NOAEL and LOAEL) should be clearly described.⁸³
7. Consistent with the level of complexity needed and if data support modeling, multiple approaches should be carried forward in the analysis and a justification must be provided for model selection.⁸⁴

⁷⁸ Ibid.

⁷⁹ EPA, Guidelines for Carcinogen Risk Assessment, 2005; see also NAS, Health Risks from Dioxins and Related Compounds: Evaluation of the EPA Reassessment, 2006, available at: <http://www.nap.edu/catalog/11688/health-risks-from-dioxin-and-related-compounds-evaluation-of-the>.

⁸⁰ EPA, Guidelines for Carcinogen Risk Assessment, 2005; Preston and Williams, DNA-reactive carcinogens: mode of action and human cancer hazard, Crit Rev Toxicol., 2005 Oct-Nov; 35(8-9):673-83, available at: <http://www.ncbi.nlm.nih.gov/pubmed/16417034>; Andersen et al., Dose-response approaches for nuclear receptor-mediated modes of action for liver carcinogenicity: Results of a workshop, Crit Rev Toxicol. 2014 Jan;44(1):50-63, available at: <http://www.ncbi.nlm.nih.gov/pubmed/24083384>

⁸¹ NAS, Science and Decisions, 2009, available at: <http://www.nap.edu/catalog/12209/science-and-decisions-advancing-risk-assessment>; Fenner-Crisp and Dellarco, 2016.

⁸² EPA, Guidelines for Carcinogen Risk Assessment; EPA, A Review of the Reference Dose and Reference Concentration Processes, 2002.

⁸³ EPA, Risk Assessment for Noncancer Effects; Fenner-Crisp and Dellarco, 2016.

8. EPA should use reliable data in lieu of default assumptions or models as a preferred approach. Any default assumptions should be clearly identified and the rationale for each must be explained including describing the impact of the default on the assessment's conclusions.⁸⁵
9. Consistent with the level of complexity needed, suitable toxicokinetic and toxicodynamic data must be used to derive more refined dose response estimates. If available, quantitative dose-response information regarding key events within a MoA should also be incorporated into the modeling.⁸⁶

⁸⁴ EPA, Benchmark Dose Technical Guidance, 2012, available at: https://www.epa.gov/sites/production/files/2015-01/documents/benchmark_dose_guidance.pdf; Fenner-Crisp and Dellarco, 2016.

⁸⁵ EPA, Guidelines for Carcinogen Risk Assessment, 2005; OMB/OSTP memorandum "Updated Principles for Risk Analysis," 2007; Fenner-Crisp and Dellarco, 2016.

⁸⁶ EPA, OPP Guidance on Tiered approach to Tolerance Assessment, available at: xx; EPA, Guidelines for Carcinogen Risk Assessment, 2005; Fenner-Crisp and Dellarco, 2016.

Appendix D: Improving Risk Characterization

ACC has identified key aspects of risk characterization that are critical to ensuring that risk evaluations are consistent with the science standards in the LCSA. This approach is fully consistent with EPA's Risk Characterization Handbook, last updated in 2000. ACC recommends that each of these key aspects be incorporated into the risk evaluation rulemaking. This will ensure that the conduct/process of developing refined risk evaluations is consistent with the high quality demanded by Sections 6 and 26 of the LCSA.

Key Aspects of Risk Characterization:

1. Risk characterization chapters should be written for both technical and non-technical audiences and be clear and understandable in describing the purpose, objectives, scope, and main findings.⁸⁷
2. Consistent with the scope and context, all potential hazards/risks should be presented for the populations and exposure scenarios of interest.⁸⁸
3. A Margin of Exposure (MOE) approach should be used to present findings. Expected and central estimates should be presented, as well as appropriate upper and lower bound values.⁸⁹
4. This section should incorporate principles of Transparency, Clarity, Consistency and Reasonableness.⁹⁰
5. EPA must ensure that the analysis presented is consistent with data that meet the relevance and quality criteria and minimizes biases related to study design, data selection, data interpretation, model choices, and conclusions.⁹¹
6. Scientific facts and science policy choices must be distinguished.⁹²
7. Confidence in conclusions/risk values should be placed clearly in the context of certainties and uncertainties, and the reasoning for use of and impact of defaults on conclusions must be explained.⁹³
8. Alternative judgments, hypotheses and models must be presented along with support explaining these alternatives. If the assessment includes only a worst-case scenario, an explanation and discussion of uncertainties must be provided.⁹⁴
9. Significant data needs are clearly identified. There is discussion of the potential impact such data might have on the assessment (i.e., value of information).⁹⁵

⁸⁷ EPA, Risk Characterization Handbook, 2000; Fenner-Crisp and Dellarco, 2016.

⁸⁸ Ibid.

⁸⁹ EPA, Risk Characterization Handbook.

⁹⁰ Ibid; Fenner-Crisp and Dellarco, 2016.

⁹¹ Ibid.

⁹² Ibid.

⁹³ Ibid.

⁹⁴ National Research Council, National Academy of Sciences, Understanding Risk: Informing Decisions in a Democratic Society 99-100, 1996, available at: <http://www.nap.edu/catalog/5138/understanding-risk-informing-decisions-in-a-democratic-society>; Fenner-Crisp and Dellarco, 2016.

⁹⁵ EPA, Risk Characterization Handbook, 2000; Fenner-Crisp and Dellarco, 2016.

10. The assessment should compare predicted or modeled health outcomes in relevant populations with actual outcomes.⁹⁶
11. The rationale for the use of defaults and models, in lieu of data, is clearly explained and justified.⁹⁷
12. Comparisons are provided to other assessments that have evaluated the same risks. A discussion of any conflicting results should be provided.⁹⁸

⁹⁶ EPA, Risk Characterization Handbook, 2

⁹⁷ Ibid.

⁹⁸ Ibid.

Appendix E: Ensuring Robust Peer Review

ACC has identified key aspects of peer review that are critical to ensuring that risk evaluations, particularly refined risk evaluations, are consistent with the science standards in the LCSA. This approach is fully consistent with EPA's Peer Review Guidance, the best practices of EPA's Science Advisory Board (SAB) as well as the recommendations from the Office of Management and Budget. ACC recommends that each of these key aspects be incorporated into the risk evaluation rulemaking. This will ensure that the conduct/process of developing refined risk evaluations is consistent with the high quality demanded by Sections 6 and 26 of the LCSA.

Key Aspects of Peer Review:

1. A documented process for peer review that matches the purpose/scope and potential impact of the assessment must be provided for public comment before the assessment begins.⁹⁹
2. Panel composition shall be consistent with best practices and ensure sufficient knowledge, expertise, and depth. Biases/perspectives shall be identified and balanced. Conflicts of interest shall be identified and disclosed.¹⁰⁰
3. All draft materials should be made available to peer reviewers and the public at the same time, allowing adequate time for review and comment.¹⁰¹
4. Peer reviewers should receive public comments in advance for adequate consideration before the peer review meeting is conducted.¹⁰²
5. At least 45 days should be provided for public comment and review of technical information.¹⁰³
6. At least one public peer review meeting will be held.¹⁰⁴
7. There will be reasonable opportunity and adequate time for public comments to be presented at the public peer review meeting. There is an opportunity for peer reviewers to engage with public commenters on the key technical issues they put forward.¹⁰⁵
8. If peer reviewers did not reach consensus, a minority opinion/report will be provided.¹⁰⁶
9. Peer reviewers, in their written report, provide responses to substantive public comments.¹⁰⁷

⁹⁹ EPA, Peer Review Handbook, 2015; OMB, Peer Review Bulletin, 2005; Fenner-Crisp and Dellarco, 2016.

¹⁰⁰ EPA, Peer Review Handbook, 2015; OMB, Peer Review Bulletin, 2005.

¹⁰¹ Ibid; Fenner-Crisp and Dellarco, 2016.

¹⁰² Ibid.

¹⁰³ This is consistent with EPA's Work Plan chemical past practices.

¹⁰⁴ EPA, Peer Review Handbook, 2015; OMB, Peer Review Bulletin, 2005.

¹⁰⁵ Ibid; Fenner-Crisp and Dellarco, 2016.

¹⁰⁶ EPA, Serving on the EPA Science Advisory Board: A Handbook for Members and Consultants, 2012, available at: [https://yosemite.epa.gov/sab/sabproduct.nsf/WebBOARD/Serving%20on%20the%20EPA%20Science%20Advisory%20Board:%20A%20Handbook%20for%20Members%20and%20Consultants/\\$File/Serving%20on%20the%20EPA%20Science%20Advisory%20Board%20SABSO-12-001.pdf](https://yosemite.epa.gov/sab/sabproduct.nsf/WebBOARD/Serving%20on%20the%20EPA%20Science%20Advisory%20Board:%20A%20Handbook%20for%20Members%20and%20Consultants/$File/Serving%20on%20the%20EPA%20Science%20Advisory%20Board%20SABSO-12-001.pdf); Fenner-Crisp and Dellarco, 2016.

¹⁰⁷ H.R. 1029, EPA Science Advisory Board Reform Act of 2015, available at: <https://www.congress.gov/bill/114th-congress/house-bill/1029/actions>.

10. Public and peer review comments are addressed and a response to comments document is released when the final assessment is released.¹⁰⁸

¹⁰⁸ EPA, Peer Review Handbook, 2015; OMB, Peer Review Bulletin, 2005; Fenner-Crisp and Dellarco, 2016.

Appendix F: Exposure Modeling Tools

Below we provide information and links to exposure modeling tools used by ECHA, and others, to help inform robust exposure evaluations.

REACH Tools:

Screening/Scoping:

ECETOC TRA (v3.1 2014): Tier 1 screening level tool to calculate the risk of exposure to chemicals to workers, consumers and the environment. Used in REACH submissions. Could be used for Scoping and Screening. <http://www.ecetoc.org/tools/targeted-risk-assessment-tra/>

CHESAR (v3.0): Tier 1 screening level tool developed by ECHA to carry out REACH safety assessments. Could be used for Scoping and Screening. <https://chesar.echa.europa.eu/>

- Incorporates:
 - TRA
 - MEASE (for catalysts)
 - RiskofDerm
 - EMKG Expo Tool

BAMA/FEA: Used to generate predicted concentration of aerosol components within workplaces following suitable time interval after spraying. <http://www.aerosol.org/regulatory-policy-affairs/product-safety/indoor-air-quality>

PetroRisk: Designed to evaluate environmental exposure and ecological risks at both local and regional scales for a wide range of petroleum products from naphtha (gasoline), kerosene, gas oils, to heavy fuel and lubricant oils as well as hydrocarbon-based solvents. The spreadsheet tool can evaluate risks associated with different stages in the product life cycle. <https://www.concawe.eu/reach/petrorisk>

Higher levels Tools:

EGRET (v2): Tier 1.5 tool developed by the European Solvent Industry Group for evaluating consumer exposure to solvents in REACH submissions. Could be used for Refined Risk Evaluation. <http://www.esig.org/en/regulatory-information/reach/ges-library/consumer-gess>

ART (v1.5): Tier 1.5 tool developed to evaluate worker exposure to inhalable mists, dusts and vapors. Could be used for Refined Risk Evaluation. <https://www.advancedreachtool.com/>

PEST : Tool developed to for refined assessments of exposure to plastic additives. Could be used for Refined Risk Evaluation. <http://www.plasticseurope.org/plastics-sustainability-14017/consumer-protection/reach.aspx>

REACT (2009): Tier 1.5 tool to estimate systemic consumer exposures to substances that are present in cleaning preparations. Could be used for Refined Risk Evaluation. <https://www.aise.eu/our-activities/product-safety-and-innovation/reach/consumer-safety-exposure-assessment.aspx>

ConsExpo (v4.1): Comprehensive Consumer Exposure model developed by RIVM (NE) in 1996. Version 4.0 has separate modules for inhalation, dermal and oral exposure. In English. Based on transparent calculation. Could be used when have consumer use that is not included in the E-FAST model.

Has been used by Canadian Government in their CEPA program and EU REACH. Could be used for Screening or Refined Risk Evaluation. <http://www.rivm.nl/en/Topics/C/ConsExpo>

Stoffenmanager (6): Tier 1.5 recognized by the Dutch Labor Inspectorate and by ECHA as a reliable tool for use in the assessment of exposure situations via inhalation as part of the Risk Inventory and Evaluation (RI&E). In addition, Stoffenmanager is also capable of assessing the risks of exposure via the skin. <https://stoffenmanager.nl/Default.aspx>

Additional Tools for Consideration:

Screening Assessments:

AIHA models: IH SkinPerm v1.2 and IH MOD are tools developed and widely accepted to estimate worker exposure. <https://www.aiha.org/get-involved/VolunteerGroups/Pages/Exposure-Assessment-Strategies-Committee.aspx>

CalTOX (v2.3): Relates the concentration of a chemical in soil to the risk of an adverse health effect for a person living or working on or near the contaminated soil. <https://www.dtsc.ca.gov/AssessingRisk/caltoc.cfm>

USETOX (v2.0): Based on scientific consensus for characterizing human and ecotoxicological impacts of chemicals in life cycle impact assessment. The main output includes a database of recommended and interim characterization factors including environmental fate, exposure, and effect parameters for human toxicity and ecotoxicity. <http://www.usetox.org/>


RAIDAR (v2.0): Model to screen and prioritize large numbers of chemicals based on hazard, exposure and risk assessment objectives for more comprehensive, higher-tiered assessments. http://www.arnotresearch.com/index_download1.html#!/page_Downloads

Refined Assessment:

IAQX (v1.1): An indoor air quality (IAQ) model that complements and supplements existing IAQ simulation programs. Inhalation only. IAQX is a Tier 2 model for advanced users who have experience with exposure estimation, pollution control, risk assessment, and risk management. <https://www.epa.gov/air-research/simulation-tool-kit-indoor-air-quality-and-inhalation-exposure-iaqx>

Appendix G: Additional Information on the ECETOC TRA

The slides attached below are from a presentation developed by Dr. Chris Money with Cynara Consulting. Please note: An explanation of many of the REACH related terms used in the slide below can be found in a Glossary on the UK health and Safety executive website: <http://www.hse.gov.uk/reach/definitions.htm>.

Cynara Consulting

ECETOC Targeted Risk Assessment (TRA) Tool: Learnings in Development and Application

Chris Money

1

Background to the TRA

- 2000 EU White Paper on Chemicals
 - All chemicals 'in use' in Europe anticipated to be registered
 - Base set of hazard data expected for all chemicals
 - No 'phase in' dates identified for different tonnage bands
- Less focus in the White Paper
 - The relationship between appropriate regulatory intervention and 'unsafe' situations
 - Need to demonstrate the safe use of chemicals
 - Registration obligations independent of risk
 - Tonnage / use / hazard profile / exposure / etc.

2

Driver for the TRA

- ECETOC* established a Targeted Risk Assessment (TRA) task force to highlight that
 - Effective chemicals regulation needs to be informed by risk
 - Exposure needs to be adequately accounted for as a key consideration when assessing and managing risk
 - The efficient acquisition and application of hazard and exposure data can only be brought about through the application of tiered, risk-informed processes
 - Reliable screening level (Tier 1) risk assessments can be undertaken by 'non-experts'
 - Appropriate decisions can be reliably made in the absence of a full 'base set' of hazard data

*ECETOC is a recognised WHO NGO and established EU scientific organisation. It is funded by over 50 companies with an interest in chemical safety.

3

The Genesis of the TRA



- EPA's Exposure Assessment Guidelines recommend completing exposure assessments iteratively using a *tiered approach* to "strike a balance between the costs of adding detail and refinement to an assessment and the benefits associated with that additional refinement"
- When conducting a tiered exposure assessment, after each iteration, the question is asked,
- **Is this level of detail or degree of confidence good enough to achieve the purpose of the assessment?**
- If the answer is no, successive iterations continue until the answer is affirmative, new input data are generated, or, as is the case for many assessments, the available data, time, or resources are depleted.
- (U.S. EPA, 1992) *Guidelines for Exposure Assessment*

4

Screening vs Refined Assessments

| | Screening | Refined |
|----------------|---|---|
| Inputs | <ul style="list-style-type: none"> • Readily available data • Conservative/default assumptions • Point estimates | <ul style="list-style-type: none"> • Site- or scenario-specific data • Realistic assumptions • Distributions of data |
| Tools | <ul style="list-style-type: none"> • Simple models and equations • Deterministic approach | <ul style="list-style-type: none"> • Complex models and equations • Deterministic or probabilistic approach |
| Results | <ul style="list-style-type: none"> • Conservative estimate of exposure • Useful for prioritization • Greater uncertainty • Variability not generally considered | <ul style="list-style-type: none"> • More realistic exposure estimate • Variability and uncertainty are better characterized |

5

The Challenge

- Can the principles of tiered risk assessment be improved such that acceptable decisions can routinely be achieved earlier in the process ?
 - Can some of the advantages of refined tools be transferred to screening models?
 - How can the application of refined models be better targeted (or streamlined)
- How to capitalize from the speed and costs of screening level assessments without being constrained by their uncertainty (in absolute terms) and inability to characterize variability?

6

Outline

- Why was the TRA activity initiated by European industry?
- How has the focus and content of the TRA changed over time? And why?
- What are considered to be the TRA's key attributes?
- Where has the TRA impacted REACH?
- How can the TRA's principles be applied to improve the process of exposure assessment?

7

Core Aims of the TRA v1 (2002)

- To **FOCUS** resources on general substance production and use scenarios that constitute a likely concern for humans or the environment
- To ensure that all decisions are based upon **RISK** and account for the relevant information that might be expected to be available
- To **SIMPLIFY** – but maintain the scientific integrity of the RA process

8

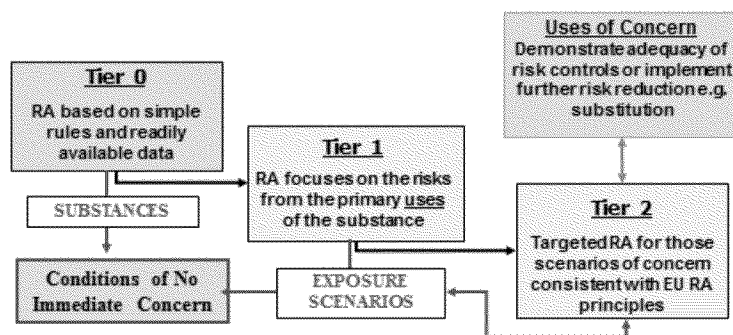
Other Aims Behind the Approach

- To develop an user friendly (product stewardship) tool that enables manufacturers and users of chemicals to readily evaluate and identify chemical SHE risks
- To clearly demonstrate the scientific integrity of the proposals
- To deliver consistency with the expectations of European regulations i.e. H&S and Chemical Agents Directive
- Align with other 'accepted' tools/concepts for exposure-driven risk assessment to facilitate harmonization across domains
- To transparently demonstrate the utility and integrity of the concepts via a web-based tool

9

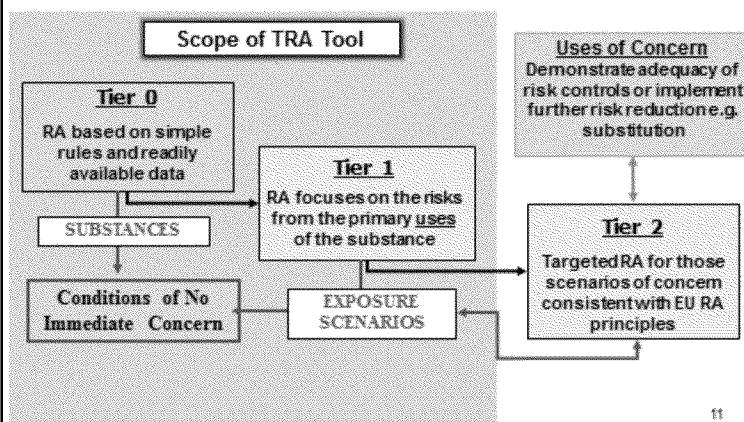
Underlying Approach of the TRA

Tiering and Targeting



10

TRA version 1 (2002-4)



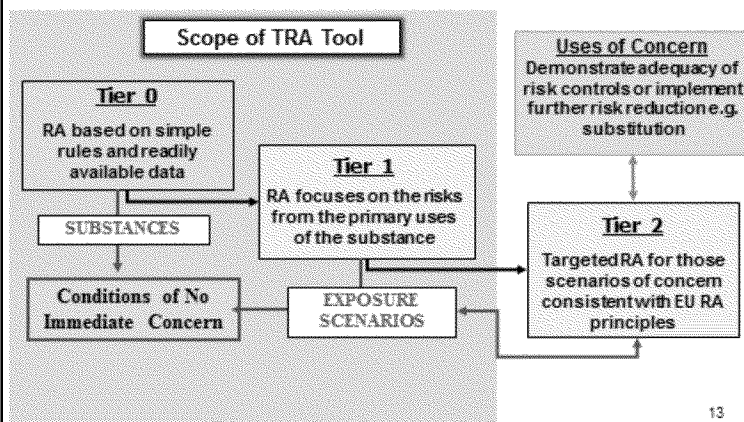
11

TRA and the Final REACH Text

- Drafts of the REACH Regulation began to appear in 2004
 - The text differed significantly from the White Paper in its 'acceptance' of tiering (for hazard); the need to demonstrate and communicate conditions of 'safe use' ('exposure scenarios'); and phase-in dates
- But the text offered no practical solutions for how the basic legal requirements might be accomplished
- Industry supported the application of the TRA in order to consistently and efficiently develop REACH RAs
 - And serve as a platform for testing emerging ideas being suggested in 'REACH Technical Guidance' e.g. Use Descriptors

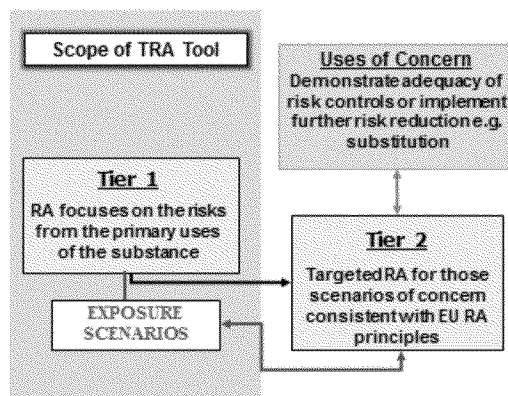
12

TRA version 1 (2002-6)



13

TRA version 2 (2007 onwards)



The significantly updated TRA consists of 2 elements

- The general philosophy of tiering and targeting risk assessments
- Optimizing the supporting TRA exposure tool for application at the Tier 1 level¹⁴

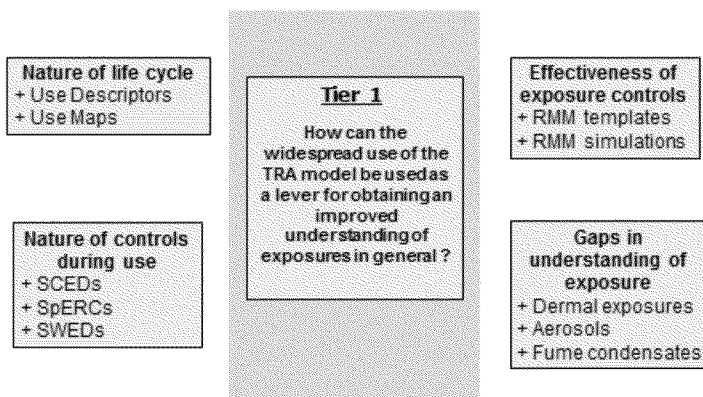
Impact of the TRA

- The TRA has been applied in ~90% of REACH CSAs
 - >20,000 substance registrations
- The TRA is used as the basis of ECHA's CSA tool (Chesar)
 - The EU regulatory community is applying the model to determine the acceptability of risks to human health and related data needs
- The TRA model demonstrates that comprehensive chemical risk assessments can be quickly, efficiently and reliably undertaken
 - Comprehensive CSAs possible in less than 2 hours
 - Covering health and the environment across the substance life cycle
 - Without requiring access to specialist consultants
- The TRA has catalyzed a number of initiatives aimed at further improving the relevance, sensitivity, efficiency and consistency of exposure/risk assessments



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TRA as a Catalyst for Targeted Action



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Enhancing the TRA's Relevance

| Key Input Elements | Purpose | Status |
|--------------------|--|--|
| Use Descriptors | Coding mechanism for enabling the consistent description of human and environmental exposures | Recently revised and updated. Managed by ECHA. Shared at OECD |
| Use Maps | Coded description of where (and how) substances are used within supply chains | Exist for most major supply chains. Managed by industry sectors |
| SpERCs | Description of the nature of environmental emissions for defined industrial processes | Exist for many major industrial processes. Managed by industry sectors. Align with OECD ECDs |
| SCEDs | Description of the nature of consumer exposures for defined uses of consumer products (and articles) | Exist for many major consumer product groups. Managed by industry sectors |
| SWEDs | Description of the nature of typical worker exposure controls for defined industrial and professional processes | Exist for principle supply chains. Managed by industry sectors. Complement GESs (see below) |
| GESs | Description of the typically encountered worker exposure controls for defined industrial and professional processes, for different substance types | Primarily exist for solvents. SWEDs are an abbreviated version of the GES. |

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Improving Process Efficiencies

How can many substances and scenarios be dealt with efficiently?

Useful aspects have proven to be:

- An inter-connected worker, consumer and environmental model
 - single data entry for substance ID and pchem
- Batch mode capabilities
 - all scenarios can be evaluated simultaneously and very quickly
- Common framework for describing exposures (GESs)
 - efficiencies in consistency, deliver relevant user exposure controls, facilitate common inputs, help with CBI, enable sensitivity analysis on control options
- Standard defaults
 - transparency and ease of use; modifications allowed within limits and subject to justification

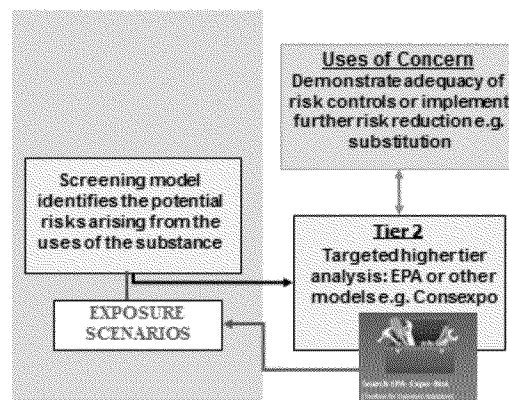
21

How the TRA Can Help in Improving the Process of Exposure Assessment

- Evidence that effective targeting can be implemented at Tier 1
- Application of an integrated model delivers major efficiency gains across stakeholders
 - Consistency across substances, sectors, uses and jurisdictions
- Alignment with IUCLID data requirements creates opportunities for wider harmonisation
 - As well as accounting for region specific variations
- Widespread use of the TRA is generating increased stakeholder confidence in its fitness for purpose
 - Testing for validation and reliability remain ongoing
- A simple risk-based tool helps identify where further data/science advisable and can be used to target (leveraged) actions

22

Enabling Effective Targeting



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Summary

- Effective targeting releases the efficiencies that tiered approaches to RA potentially present
- Key to targeting are workable schemes for describing use
 - Comprehensive, understandable, pragmatic, implementable
 - Global harmonisation is an area of discussion at OECD
- The TRA has demonstrated that
 - Reliable regulatory decisions can be made with the minimum of unnecessary data
 - Risks can be assessed in a tiered, integrated approach and communicated in a manner that is relevant and understandable
 - Engagement within and across industry/stakeholders is essential for ensuring effective and relevant decision making

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What is ECETOC ?

- WHO recognized NGO funded by over 50 major companies with an interest in the safe use of chemicals
- Track record of positive scientific engagement with EU regulators (and OECD)
 - Hazard assessment; Classification criteria; environmental fate
- Not viewed by Commission/stakeholders as having vested interests
 - Recommendations seen to be predominantly based on science
- Consensual approach to problem solving
 - Transparency in demonstrating rationale for preferred solutions
- Willingness and ability to think outside the box
 - Avoid constraints of historical 'mistakes'
 - Seed the introduction of new ideas and approaches

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TRAv1 Web Tool

THIS SITE WILL SHORTLY BE UPDATED TO REFLECT AGREEMENTS BETWEEN IT AND THE PUBLISHED FINAL TRA REPORT

ECETOC Targeted Risk Assessment <https://www.ecetoc-tra.org>

Welcome to the ECETOC Targeted Risk Assessment Web Tool

General Menu

- Welcome
- Add new substance
- Search substances

Overview

- Start
 - Chemical identity
 - Physical - Chemical
- Health
 - Exposure potential
 - Hazard data
 - Results
- Workers
 - Exposure
 - Hazard
 - Chemical assessment
 - Results
- Consumer
 - Exposure
 - Hazard
 - Assessment factors
 - Results
- Environment
 - Introduction
 - Fate and effects

Introduction

This web-based system is the initial electronic implementation of the principles from an ECETOC Task Force on Targeted Risk Assessment* which was formed to propose a Risk Assessment process within the context of the EU's New Chemicals Policy. It contains elements for both human health and environmental risk assessment.

It is not intended to be a complete working model, but a demonstration of the practicality and functionality of the ECETOC Tiered Risk Assessment approach, Tier 0 to Tier 1, resulting in a Chemical Safety Report. As such, not all the functionality is enabled (links to other models) and some options are not yet available. It is intended to develop the tool progressively and use it as a validation exercise.

The basic principles and flow of the Tiered and Targeted Risk Assessment approach are given in a brief description of the process.

Basic Principles of Targeted Risk Assessment

Instructions for data input and risk assessment

The TRA web Tool is designed so that it takes the user through a series of the logic steps for the tiers of the risk assessment. It is transparent to the user what has happened at each stage of the process. As a screen builds showing the data / results so far.

- Data entry is simple with drop down and selection boxes wherever possible.
- Instruction for each stage is (will be) available.
- Please use the tool to enter data and give feed back to the Task Force on any aspect. An email link is provided.

Data input requirements

To see a list of what data will be required for each stage of the risk assessment process [click here](#)

Confidentiality

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